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ACUTE APPENDICITIS COMPLICATING THE ACUTE INFECTIOUS DISEASES OF CHILDHOOD*

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ACUTE appendicitis in children displays certain features in its pathology, clinical course, diagnosis and treatment, which vary considerably from those of the disease in adults. The development of appendicitis during the course of one of the acute infectious diseases or in a child exposed to them further complicates the problem.

It seems to be commonly accepted opinion that certain of the contagious diseases, such as measles, tend to be complicated by a higher than normal incidence of appendicitis, that the diagnosis of acute appendicitis is apt to be rendered more difficult or masked by the presence of one of these contagious diseases, and that the mortality and morbidity of acute appendicitis is higher when so complicated than that of appendicitis occurring alone.

Most reviews of the problem of appendicitis give little statistical consideration to these aspects. Ladd and Gross[1] mention an apparently increased frequency of acute appendicitis in children with measles. Babcock[2] also states that "infections that produce general lymphoid hyperplasia such as measles, scarlet fever — often precede appendicitis." Scott and Ware,[3] on the other hand, in a more recent appraisal of appendicitis in children, believe that no causal connection exists between the acute contagions and other upper respiratory infections and acute appendicitis.

A check on the validity of these impressions was undertaken in a study of cases of acute appendicitis in children under twelve years of age seen during a twenty-one-year period, recently ended, at the Haynes Memorial, the infectious disease unit of the Massachusetts Memorial Hospitals in Boston. This included a group of 100 consecutive cases in which the appendix was examined.

PATHOLOGICAL FINDINGS

The pathologic changes found in these cases are listed in Table 1. Ninety-six patients (96 per cent) demonstrated some stage of acute appendicitis. In 61 of these the appendix was perforated, and some degree of peritonitis existed. Although sufficient evidence of localization to warrant the use of the term "abscess" was noted in 17 cases, we have found this an unsatisfactory classification because in children appendiceal peritonitis tends to localize poorly. Clinically, they may well be far sicker than the term "appendiceal abscess" suggests when the condition is encountered in an adult, and often require as vigorous and prompt treatment as cases without any tendency to localization of the peritonitis. Scott and Ware[3] recognized this situation in classifying acute appendicitis at the Children's Hospital in Boston and grouped their cases as "acute, unruptured" and "acute, ruptured with local or diffuse peritonitis." In more than 1300 cases reported by them, perforation of the appendix had occurred in 44.8 per cent, as compared with 64 per cent in our series.

TABLE 1. *Relation Between Type of Appendicitis and Mortality Rate.*

TYPE	NO. OF CASES	NO. OF DEATHS	MORTALITY %
Acute (with no rupture)	35	1	2.8
Acute (with rupture and local or diffuse peritonitis)	61	7	11.5
Pinworms only	2	0	0
Normal appendix	2	0	0
Totals	100	8	
Average			8.0

Only 4 cases of the 100 in this group revealed no acute inflammation on microscopical examination. Pinworm infestation was the only finding in 2 of these cases, although the symptomatology and physical findings were those of acute appendicitis. In the remaining 2 cases entirely negative pathological findings indicated errors in the clinical diagnoses.

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Association of Infectious Diseases with Appendicitis

Table 2 shows the distribution of the various infectious diseases associated with acute appendicitis in this series.

Eighty-eight of these children actually had an infectious disease, and the remaining 12 had been exposed to or were thought to be in the prodromal stage of one at the time of admission. The three largest and nearly equivalent groups of cases of appendicitis correspond to the three most common diseases, scarlet fever, measles and chicken pox, which accounted for 77 of the 88 actual cases of infectious disease in this series. In Table 2 are listed also the admission totals for the various contagions at the Haynes Memorial over the twenty-one-year period, 1927 to 1948. The experience with scarlet fever is revealed as much greater than that with any other disease, because it has been the policy of the Massachusetts Department of Public Health to encourage routine hospitalization of all patients with scarlet fever whenever possible.

Table 2. *Twenty-One Years' Experience with Appendicitis in Infectious Diseases (Children under Twelve Years).*

Disease	Cases of Appendicitis (Haynes Memorial)	Total Cases of Infectious Disease	
		Haynes Memorial	Massachusetts
Scarlet fever	23	12,192*	221,365
Measles	25	11,451	504,593
Chicken pox	20	609	254,371
Pertussis	11	868	181,135
Rubella	3	—	—
Mumps	6	1,043	177,359
Miscellaneous	4	—	—
None	12†		
Total	104‡		

*This figure represents 5.5 per cent of all reported cases of scarlet fever in Massachusetts.

†These children, although exposed, failed to develop a clinical contagion.

‡Four children had two of the contagious diseases.

The 23 cases of appendicitis occurring in the large group of 12,192 patients with scarlet fever admitted to the hospital represented an incidence of only 0.2 per cent, which was probably a fair sample of the statewide experience. It is interesting to note that the approximate incidence of appendicitis in all children under the age of ten years calculated from mortality tables for the year 1947 in Massachusetts was also 0.2 per cent.*

Total admission figures for measles, chicken pox, pertussis and mumps at the Haynes Memorial are seen as relatively small compared with the total reported cases for the state (data supplied by the Massachusetts Department of Public Health) since admissions for these diseases were chiefly because of complications. Similar incidence rates for appendicitis occurring in these diseases, therefore, cannot be calculated on any sound statistical basis, although it seems apparent from a study of Table 2 that such rates would probably be no higher than those for appendicitis in scarlet fever.

Our interpretation of these data is that, contrary to traditional opinion, children with scarlet fever and other common contagious diseases show no greater tendency to the development of acute appendicitis than otherwise normal children do.

Influence of Infectious Diseases on Diagnostic Accuracy

The diagnosis of acute appendicitis in a child already ill with an infectious disease may be a very difficult one to make, as every physician who faces this problem will testify. Statistically, the effect of such diseases on the accuracy with which coexisting appendicitis could be diagnosed prior to hospital admission probably is best reflected in certain data presented in Table 1. Sixty-one per cent of the acutely inflamed appendixes in our series were found to have ruptured, whereas only 44.8 per cent were ruptured in the Children's Hospital series. This higher incidence of rupture apparently cannot be attributed to a predominance of younger patients, since only 41 per cent of the ruptured appendixes in our series were found in children under the age of six years, whereas the figure derived from the Children's Hospital series was 53 per cent. Further analysis of the data suggests also that our high percentage of perforation cannot be explained by a postulated acceleration of the appendiceal inflammation by the infectious disease. The average period of delay from onset of symptoms to hospitalization for simple acute appendicitis was 1.4 days, but for ruptured appendix with local or generalized peritonitis, it was 3.1 days. These delays are essentially the same as those encountered in children with appendicitis uncomplicated by such diseases, as comparison with figures derived from the large series at the Children's Hospital will reveal. Calculations from the data of Scott and Ware[3] show average delays of 1.5 and 3.4 days for the corresponding stages of appendicitis. Undoubtedly, masking symptoms and signs such as abdominal pain, fever, nausea and vomiting and respiratory complaints, which are often part of the presenting picture of the acute contagion, have made the diagnostic problem more difficult for the referring doctors. The telltale signs of peritonitis, when these developed, usually could be distinguished readily enough from those of the contagion so that the delay in these cases after rupture was not of unusual duration. Five children, however, all with ruptured appendixes, were referred to the hospital without any suggestion of this diagnosis but merely because the courses of their infectious diseases seemed unfavorable.

*This calculation is based on an assumed mortality rate of approximately 5 per cent for acute appendicitis in this age group.

After admission to the hospital diagnosis was made earlier, of course, by more elaborate facilities, in addition to the fact that, in most cases, signs were better established. It is not surprising, then, that a diagnosis of acute appendicitis leading to early operation could be made promptly after admission by the resident staff and consultants in 84 of 100 cases. In an additional case, operation was deliberately delayed for eighteen hours in an attempt to improve the condition of the critically ill and toxic child. Operation was delayed for twelve hours or more in 14 children because of uncertainties in diagnosis, but in only 9 of these was a sufficiently serious appendicitis found to have made this delay of any hazard to the patient. The entire series included only 1 case in which death resulted after continued failure to diagnose a ruptured appendix clinically in the hospital. These statistics, however, fail to indicate adequately the very real difficulty encountered occasionally at the Haynes Memorial in making the diagnosis of appendiceal peritonitis in very young children.

An undetermined number of children, possibly 50 or more, were admitted during the same period covered by this study with a question of acute appendicitis that could not be confirmed by further observation and study at the hospital. Lymphadenitis or lymphoid hyperplasia, acute enteritis, mumps oophoritis, pancreatitis, referred pain and even constipation were variously thought to account for the clinical pictures simulating appendicitis in these cases.

Cases with Delay in Hospital Diagnosis

As noted above, in 9 children with established and serious appendicitis, operation was delayed more than twelve hours from time of admission owing to difficulties in diagnosis. In 1 of these, which resulted in death, there was a probable delay of four days after the onset of appendicitis in a child who was convalescing in the hospital from scarlet fever. When actual pain and tenderness developed, operation was performed immediately, and a small abscess was encountered. The child did well initially but died thirty days later from meningitis and septicemia, which did not seem to bear any direct relation to the appendicitis. Ruptured appendixes and varying degrees of peritonitis were found in half (4 cases) of the other 8 patients in this group. Five of these children had active chicken pox. None of this group of 8 died, however.

In summary, it seems fair to say that the diagnosis of acute appendicitis in the hospital was made somewhat more difficult by the coexistence of the infectious diseases. Serious delays in diagnosis occurred in 9 cases, or about 10 per cent of the total, several patients being very sick children and difficult therapeutic problems. Fortunately, there was only 1 fatal case in this group. No data are available for comparison on the percentage of diagnostic delay in children with appendicitis uncomplicated by other diseases, although it must be appreciable.

Analysis of Deaths

There were 8 deaths in the whole series of 100 cases. One of these, mentioned above, resulted from a diagnostic error. This occurred in C. M., a three-year-old girl, who had been exposed to pertussis and who entered the hospital on November 6, 1937,

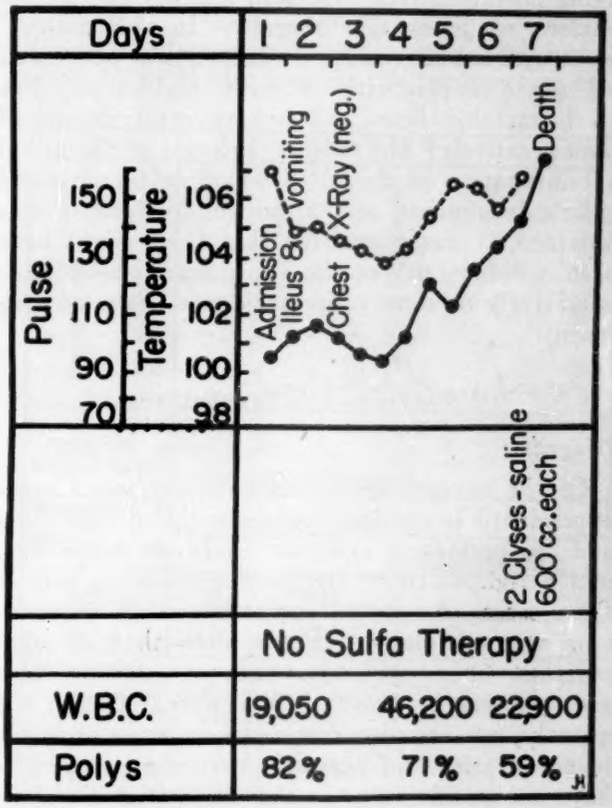

Figure 1. *Clinical Course in a Thirty-Four-Month-Old Girl with Undiagnosed Appendiceal Peritonitis.*

after forty-eight hours of fever and vomiting in a very toxic state with distended abdomen and clinical signs of pneumonia. Although she was observed carefully and seen by two surgical consultants, the clinical findings never seemed adequate to warrant a diagnosis of acute surgical condition of the abdomen (Fig. 1). Conservative therapy, which did not include sulfonamides, was ineffectual, and the child died on the seventh day after admission; autopsy revealed a ruptured appendix and generalized peritonitis but no pneumonia.

The other 7 deaths in this series came after operation. In 1 of these children (referred to above) death occurred on the seventy-eighth hospital day, being due to a streptococcal meningitis following bilateral mastoiditis; this case, in all fairness, could be excluded from the deaths caused by appen-

dicitis. Five other children died after operation, apparently from peritonitis, including the child who was given conservative therapy eighteen hours before operation, in an effort to improve his general condition. It seems significant that all 5 of these patients were treated in the years prior to so-called "modern therapy" when adequate fluids and electrolytes were not administered parenterally, stomach and intestinal intubation was not employed, and there was no chemotherapy. The descriptions of these cases were those of intractable ileus, dehydration and toxicity. Only 1 child among the 7 dying postoperatively was seen recently enough for modern supplementary therapy. In this patient, a girl with rubella, an appendectomy was performed for acute appendicitis without perforation, but an intractable ileus and hyperpyrexia developed postoperatively. She failed to respond to parenteral administration of fluids, sulfonamide therapy and gastric intubation, and although no autopsy was obtained, it was postulated that there might have been a "blow-out" of the appendiceal stump postoperatively or some other accidental cause of peritonitis.

Clinical Observations

Diagnosis

Of the several symptoms that suggested acute appendicitis in children, *pain* was the most obvious and the presenting symptom in 78 per cent. This was a right-sided or right-lower-quadrant pain in most cases. An initial periumbilical or epigastric pain was complained of less often than in adult patients. Other symptoms such as vomiting, fever and changes in bowel habits were reported frequently, but are such common symptoms of scarlet fever, measles and pertussis that they seemed to have no specific value in the differential diagnosis.

Certain physical signs seem to have been even more helpful than the history of pain in our series. *Local tenderness* over the area of the appendix was observed in the majority of children with acute appendicitis. *Spasm* was an informative sign at times in older children but rarely in very young children, probably because of voluntary splinting, crying and poor co-operation in general. We have listened carefully for intestinal peristalsis in recent years, and this has proved quite helpful at times in differentiating acute appendicitis from acute enteritis. Peristalsis was usually normal or diminished to auscultation in appendicitis, but almost invariably hyperactive in acute enteritis. The production of pain by coughing and rebound tenderness, probably explainable as resulting from the agitation of inflamed peritoneal surfaces, have been quite impressive and helpful diagnostically in some of the older children. Abdominal distention and ileus (in the absence of obvious reflex sources of this disturbance, such as pneumonia) was found frequently in appendiceal peritonitis and was, in fact, suggestive of this diagnosis. Rectal examination has been of little help to us in the diagnosis of acute appendicitis except for the identification of a palpable mass in the pelvis. After one or more digital rectal examinations small children have become so apprehensive and poorly relaxed that it has been impossible to localize tenderness rectally.

The body temperature and the pulse rate have been influenced sufficiently by the contagious diseases present in many cases to be of little help in the diagnosis of the acute appendicitis.

The white-cell count and the differential count have also been confusing at times. In several cases of acute appendicitis developing in children with measles, for example, low total white-cell counts with mild neutropenia were found.

Discussion

Surgical Management

It seems generally agreed that the diagnosis of acute appendicitis without perforation in a child, as well as in an adult, calls for early operation. This should never be so rushed, however, that sufficient time is not taken to restore disturbed fluid and chemical balances and to place the child on stomach drainage if there has been vomiting or evidence of ileus. Scott and Ware[3] and others[1, 4, 5] emphasize the need of this preparation. The coexistence of one of the infectious diseases does not alter this indication for early surgery in our experience, except that the child may require a little longer preoperative preparation because of exposure to a longer period of toxicity and dehydration.

The time of operation is undoubtedly a more debatable question in cases of ruptured appendix with peritonitis. Conservative management of appendiceal peritonitis has proved valuable in many adult cases in the past, although undoubtedly the utilization of the more modern methods of treatment, particularly antibacterial therapy, must be altering the picture a great deal, permitting earlier surgery. We believe that continued conservative treatment of appendiceal peritonitis rarely is indicated in children — a belief based on personal experience as well as the testimony of several others.[1, 3, 4]

For various reasons localization of the peritonitis cannot be relied on as effectively in children as in many adults. Anatomically, children do not have a sufficiently developed omentum and other peritoneal appendages available to aid in localization of a peritonitis. In addition, the appendix itself is far larger and longer in relation to the intestines and peritoneal structures than that in the adult, and the cecum often seems more mobile, creating greater potentialities of contamination by repeated leakage of pus and bowel content from a perforated appendix.

From a therapeutic point of view small children seriously ill with appendiceal peritonitis may be very difficult to handle. Fluid and electrolyte depletions develop rapidly. The veins are difficult to find and to keep cannulated for the necessary administration of replacement fluids. It is difficult to keep gastrointestinal tubes down and properly functioning.

A recent case illustrates the failure of conservative handling of appendiceal peritonitis despite all modern therapeutic efforts:

R. McA., a 2-year-old boy, was admitted to the Haynes Memorial Hospital in September, 1947, with a diagnosis of poliomyelitis, which was confirmed by spinal-fluid findings and clinical observations. For the first 2 days in the hospital his course was approximately that of other patients being treated at the same time. He had only a slight fever and little toxicity but presented a partial paralysis of the trunk and extremities. Two days after admission abdominal distention, with a quiet abdomen and some temperature and pulse rise, developed. Physical and x-ray signs of bronchopneumonia were present. He did not complain of specific abdominal pain, and there seemed to be no definite tenderness. The distention became more severe, and it was thought that he probably had the type of paralytic ileus not infrequently associated with pneumonia and sometimes with severe poliomyelitis. A Miller–Abbott tube was passed, adequate

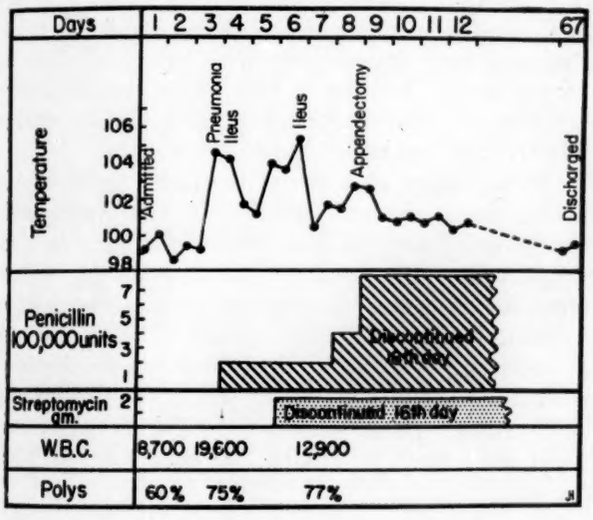

FIGURE 2. *Clinical Course in a Two-Year-Old Boy with Poliomyelitis and Perforated Appendix.*

fluids administered parenterally and intramuscular injection of penicillin started. The patient improved somewhat but had a recurrence of distention in 24 hours and again became very toxic. On the 4th day after the onset of the original distention a mass could be felt in the right lower quadrant of the abdomen. He was seen in consultation by one of us (K. B. L.), and it was thought that he had peritonitis from a ruptured appendix, with partial localization. Operation was performed promptly through a small McBurney incision. A large collection of pus was drained from the upper portion of the pelvis and the right lower quadrant, and the poorly formed walls of the abscess cavity, formed largely by adjacent bowel, collapsed. The appendix lay directly beneath the incision and was removed very simply after ligation of its base. Only the abdominal wall superficial to the peritoneum was drained. Postoperatively, the child improved dramatically. The temperature fell to practically normal in less than a day; he had spontaneous bowel movements about 2 days postoperatively and improved rapidly from then on. The clinical course is demonstrated in Figure 2.

In this case dramatic improvement and recovery followed the drainage of the septic process and removal of the appendix, although until that time the patient was getting rapidly and steadily sicker despite heavy doses of penicillin and streptomycin, adequate fluids, transfusions, oxygen, gastrointestinal intubation and other supportive therapy.

It has been our general experience in cases of ruptured appendix with peritonitis in children that early removal of the appendix, as a source of continuing contamination, with aspiration of available pus, when supplemented by antibacterial and other appropriate therapy, almost always results in prompt improvement in the patient's condition and in recovery. Figure 3 shows the temperature chart

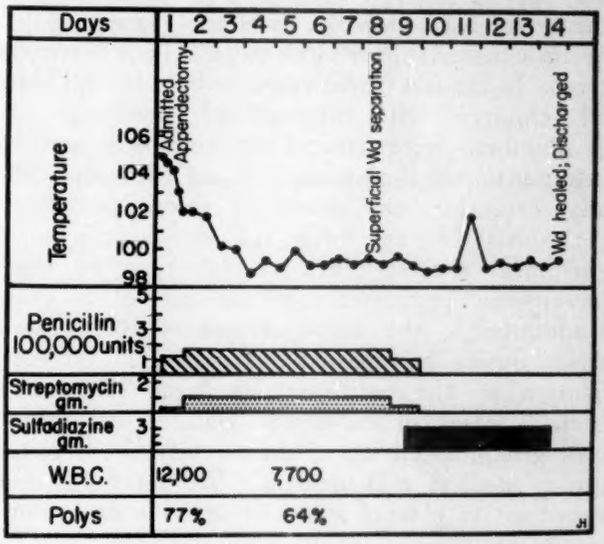

FIGURE 3. *Clinical Course in a Six-Year-Old Boy with Chicken Pox and Appendiceal Peritonitis.*

and clinical data in J. N., a six-year-old boy, seen in July, 1947, whose course was typical of cases of this sort.

Anesthesia

Inhalation ether has been the preferred anesthetic, since this seemed easiest to administer to small children and probably the safest, yielding adequate relaxation when properly given. Spinal anesthesia has been used in a few older children.

Surgical Technic

The McBurney incision has been used almost exclusively in the past three years and has proved generally satisfactory in appendicitis in children, simply for removal of an acute appendix or when the condition is complicated by peritonitis or abscess. This incision has provided adequate access to the appendix without great disturbance of the intestines, and the spreading of contaminated material. It is interesting to note that when the type of incision was recorded for cases of perforated appendix in this series, 36 rectus incisions were

made with 1 case of extensive wound slough and 1 of serious wound infection, whereas there was only 1 deep wound infection in 21 McBurney incisions. In the infected McBurney incision the abdominal wall had not been drained despite contamination by intraperitoneal pus. It is only fair to say that most of the McBurney incisions were made during the era when chemotherapy was administered. We follow the practice of doubly ligating the base of the appendix and tying over it a portion of mesoappendix or any epiploic fat tab locally available and have had no proved case of leakage from the stump or other stump complications. We do not consider it necessary or desirable to drain the peritoneal cavity, except in the rare case in which it may not be possible to remove the appendix or to secure its base properly, or when a great deal of necrotic material in relation to an abscess is encountered. In the last three years covered by this study all children with appendiceal peritonitis, 12 in number, were treated in this way without intraperitoneal drains, and in no case was there any extension or failure of resolution of the peritonitis or any case of subsequent intraperitoneal abscess that, it seemed to us, might have been prevented by the use of a drain. Undoubtedly, the vigorous use of antibacterial drugs during this period has helped in the sterilization of the peritoneal exudate. There have been 2 cases of cul-de-sac cellulitis in this recent group, and both of these resolved completely under medical management. We have found it expedient to place a soft-rubber tissue drain down to the peritoneum in all cases of peritonitis. The properitoneal fatty tissue appears to be quite vulnerable to infection, and a deep abdominal-wall abscess with cellulitis is likely to originate in this area if this drainage is omitted.

Antibacterial-Drug Therapy

The sulfonamide drugs, penicillin and streptomycin undoubtedly have been valuable in assisting the localization of appendiceal peritonitis and the control of complications, such as pneumonia. In a group of 26 children with appendiceal peritonitis, prior to the advent of this treatment, there were 5 deaths, all due to sepsis, whereas in 21 recent cases, treated in the era of antibacterial drugs, only 1 death occurred. Sulfanilamide was the only form of chemotherapy available for administration to this particular patient. Although sulfanilamide was implanted intraperitoneally in several cases of this series, we now prefer to administer the sulfonamide drugs, when indicated, by the intravenous or oral routes, believing that equivalent or better control of peritonitis can be obtained with greater safety. Much credit for the striking improvement under chemotherapy, however, must be given to the other aspects of modern supportive therapy in such sick surgical patients. Our present policy is to use heavy penicillin therapy by frequent intramuscular administrations supplemented by sulfadiazine or streptomycin in the more toxic children with peritonitis, particularly if the cultures demonstrate susceptible organisms.

Summary and Conclusions

An analysis of the experience with acute appendicitis at an active infectious-disease hospital indicates that there is no apparent predisposition to the development of acute appendicitis in children with the common infectious diseases.

The diagnosis of acute appendicitis was rendered somewhat more difficult by the coexistence of other diseases, but not to the point where any large number of diagnoses were missed or necessary surgical treatment postponed beyond the critical period.

A much higher incidence of ruptured appendix with peritonitis was found in this series (64 per cent) than in a group from a large children's clinic admitting very few patients with infectious diseases (46 per cent). It seemed likely that this difference was due to greater difficulties in diagnosis during the period before admission to the hospital.

The mortality of 8 per cent in this series of 100 cases is high. In our opinion, it was attributable only in small part to diagnostic difficulties and the complications imposed by the coexistence of the infectious diseases. In the twenty-one-year period covered, 7 of the 8 deaths occurred before the use of modern treatment, including chemotherapy, parenteral administration of fluids, intubation and transfusions. These deaths were due to sepsis and might have been prevented had such therapy been available.

We are indebted to Dr. Louis Weinstein, physician and chief of service, Haynes Memorial Hospital, for his cooperation and helpful criticisms in the preparation of this paper.

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THE EVOLUTION OF INTERCAPILLARY GLOMERULOSCLEROSIS*

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IN 1936, Kimmelstiel and Wilson[1] described a diffuse, microscopic lesion in the kidneys of 8 middle-aged and elderly diabetic patients with hypertension, profuse albuminuria and generalized edema. The abnormality was termed "intercapillary glomerulosclerosis" and consisted of striking changes in the intercapillary tissue characterized by large hyaline masses confined to the centers of the glomeruli or glomerular lobules. Less severe degrees of this hyalinization were also reported. These observations have been confirmed and extended by many authors,[2-8] and the subject has recently been reviewed by Kimmelstiel and Porter.[9]

The available published data are inconclusive concerning the period necessary for the evolution of the lesions of intercapillary glomerulosclerosis from their inception to the advanced stage. An opportunity was recently provided to study a patient who had had diabetes mellitus for the last eight years of her life. Four years before death a nephrectomy had been performed for a suspected neoplasm. Two years before death — that is, six years after the onset of diabetes — massive albuminuria developed. Comparative histologic study of the surgically removed kidney and that obtained at autopsy provided a basis for elucidating the development of the renal disorder and the correlation of the latter with the clinical picture.

CASE REPORT

R. S. (B. I. H. 30736), a 61-year-old married woman, had been told in 1935 by her family physician that her blood pressure was elevated. In March, 1936, she complained of loss of weight, weakness, pruritus vulvae, polyuria and polydipsia of 9 months' duration and of repeated attacks of gall-bladder colic without jaundice for 15 years. The blood pressure was 170/106. The urine gave a ++++ test for sugar and contained no albumin. In April she was hospitalized for regulation of the diabetes mellitus. The left kidney was palpable; retrograde pyelography revealed a "large cyst in the lower pole." Intravenous cholecystography revealed no filling. The blood pressure was 166/100 and dropped to 110/70 during the rest of her hospital stay.

TABLE 1. *Results of Urinalyses.*

DATE	NUMBER OF SPECIMENS EXAMINED	SPECIFIC GRAVITY	ALBUMIN	SUGAR	REMARKS
March 1936	2	1.008 and 1.028	0	0 and ++++	—
April and May 1936	11	1.008 to 1.030	0	0 to ++++	Hospitalization for cholecystectomy
September 1937 to March 1940	3	1.003	0	0 to ++++	—
April 1940	2	1.010 and 1.012	0	0 to ±	Hospitalization for nephrectomy
December 1940	3	1.006 to 1.012	0	0 to +++	Hospitalization for respiratory infection
June 1941	1	1.002	0	0	Hospitalization for bilateral saphenous-vein ligation
July and August 1941	39	1.002 to 1.026	+ to ++	0 to ++++	Hospitalization for sepsis
September 1941 to May 1942	54	1.002 to 1.016	0	0 to +	Hospitalization for sepsis
July 1942 to November 1942	5	1.010 to 1.026	0	0 to +	
December 1942	1		++		—
January 1943 to January 1944	8	1.008 to 1.020	++++	0 to +	—
March 1944	1	1.018	++++		—
April 1944	1		++++		—
May 1944	1		++++		—
August 1944	5	1.010 to 1.020	++++	0 to +	Hospitalization (terminal)

The diabetes was readily controlled with moderate doses of regular insulin. The urinary findings are recorded in Table 1. Cholecystectomy was performed, and cholelithiasis and chronic cholecystitis were found.

After discharge the patient did well on a diet and moderate doses of protamine zinc insulin. Repeated urine examinations revealed no albumin. In April, 1940, because the left kidney had increased in size, a renal neoplasm was suspected, and nephrectomy was performed. The diabetes remained well controlled. The blood pressure ranged between 110/70 and 150/80. Two urine examinations revealed no albumin. At operation a grape-fruit-sized renal cyst was found; the kidney without the cyst weighed 135 gm. The significant microscopical findings are listed in Table 2.

Thereafter she again did well until December, when she was readmitted for several days because of an upper respiratory infection. Three urine examinations revealed no albumin. An electrocardiogram was normal. The diabetes remained readily controlled with diet and small amounts of insulin. In February, 1941, for the first time she showed early bilateral lenticular opacities. The disks and vessels were normal; there were no hemorrhages or exudates.

In June, 1941, bilateral high ligation of the saphenous veins was performed for varicose veins. The blood pressure was 160/86. Again, the urine was normal (Table 1). Three weeks postoperatively, after bleeding in the incision in the left groin, the patient experienced fever, chills and severe localized inflammation for which she was again hospitalized (Table 1). Chills and fever continued during the 1st week, and blood cultures revealed *Staphylococcus albus*. For the first time

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albuminuria was noted. After 5 days of oral and parenteral administration of sulfathiazole, the drug was omitted because of microscopical evidence of hematuria. On August 6, a large abscess in the left groin was incised and drained; the pus revealed *Staph. albus*. On August 8 perivenous abscesses of the left thigh and calf were drained, and the left greater saphenous vein was excised. She felt well until August 30, when chills, fever and tenderness in the left flank indicated sepsis. Sulfadiazine was administered for 1 month. Albuminuria had disappeared, and except for occasional microscopical evidence of hematuria and slight glycosuria the urine was normal. On September 8 an abscess in the posterior aspect of the left thigh was incised and drained, and 3 days later the left common iliac vein was ligated after a septic clot was found in the left external iliac vein. The septic course continued and bilateral necrosis of the heels and a decubitus ulcer of the sacrum developed. Sulfadiazine was again given for 2 weeks, during which albuminuria and hematuria were absent. After excision of the necrotic tissue over the sacrum the patient became afebrile, and the ulcers of the heels disappeared. On January 24, 1942, an abscess under the nail of the right great toe was drained and healed slowly. Bilateral foot drop developed; the knee jerks, ankle jerks and vibration sense were absent. Insulin was not necessary during the 10-month period of hospitalization. She was discharged on May 1, 1942.

She was checked at monthly intervals during the remainder of 1942, and occasionally thereafter. Her vision was 20/100 on the right and 20/40 on the left. The neurologic manifestations showed little improvement. The sacral lesion responded slowly but was not completely healed until September 21, 1943. Throughout this period, the blood pressure was approximately 160/90.

Gradually, her vision became impaired until on April 22, 1944, it was 8/200 on the right and 4/200 on the left. Numerous small lenticular and vitreous opacities were seen. Ophthalmoscopic examination revealed for the first time slight blurring of both disk margins and small hemorrhages intermingled with clump-like, white exudates of different sizes between the disks and macular regions; in the left fundus between the disk and macular region was a large, homogeneous, yellowish-white area of about 4 disk diameters over which the vessels were not seen. On May 13 further reduction in vision was found (4/200 on the right and 3/200 on the left).

After her discharge from the hospital in May, 1942, the diabetes was mild and insulin was unnecessary. Six months later massive albuminuria first appeared (Table 1). In June, 1944, she experienced pain in the left anterior portion of the chest. She was hospitalized on August 5 because of sudden onset of cough, dyspnea, fever, weakness, drowsiness, nausea and vomiting. Examination revealed fever, basal pulmonary rales and a blood pressure of 165/80. The elevated temperature subsided promptly after penicillin therapy. Glycosuria was readily controlled with 20 units of protamine zinc insulin daily. The blood nonprotein nitrogen fluctuated between 46 and 79 mg. per 100 cc. The serum protein was 5.9 gm. per 100 cc. An electrocardiogram revealed normal rhythm, with a rate of 65, ventricular premature beats, a small Q wave in Lead 3 and inverted T waves in Leads 2, 3 and 4. Lethargy, incontinence of urine and recurrence of sacral decubitus ulcers characterized the remainder of her hospital course, and she died on August 20.

Autopsy (A44-77), performed 4½ hours after death, showed minimal edema of the ankles. No fluid was present in the pleural or peritoneal cavities.

The heart weighed 340 gm. The coronary arteries were sclerotic. The left ventricular wall was 1.3 cm., and the right 0.5 cm. in thickness. At the anterior aspect of the apex of the left ventricle an area of soft myocardium was overlaid by a friable mural thrombus. Microscopical examination of the heart revealed patchy fibrosis throughout the myocardium and an organized endocardial thrombus overlying a completely healed infarct at the apex.

The pancreas was normal on gross examination and microscopically revealed occasional hyaline arteriolar change. The lungs showed patches of bronchopneumonia. The spleen was normal in size and weight and contained a small infarct. The liver and adrenal glands were normal on gross and microscopical examination. The duodenum ex-

TABLE 2. *Microscopical Renal Findings.*

FINDING	LEFT KIDNEY REMOVED IN 1940*		RIGHT KIDNEY REMOVED AT AUTOPSY IN 1944†	
	PERCENTAGE OF GLOMERULI STUDIED	TOTALS	PERCENTAGE OF GLOMERULI STUDIED	TOTALS
Severe lesions of intercapillary glomerulosclerosis:				
1 to 5 or more large (20 to 120 microns in diameter) discrete hyaline globular masses in addition to diffuse thickening of the axis of the glomerulus, with or without small irregular hyaline masses				
5 or more large discrete hyaline globular masses per glomerulus	0.0		0.5	
4 discrete hyaline globular masses per glomerulus	0.0		2.0	
3 discrete hyaline globular masses per glomerulus	0.0		6.0	
2 discrete hyaline globular masses per glomerulus	0.0		17.0	
1 discrete hyaline globular mass per glomerulus	0.4‡	0.4	22.0	47.5
Moderately severe lesions of intercapillary glomerulosclerosis:				
Small, irregular hyaline masses in midst of diffuse thickening of axis of glomerulus	0.0	0.0	25.0	25.0
Mild lesions of intercapillary glomerulosclerosis:				
Diffuse thickening of axis of glomerulus	0.0	0.0	15.0	15.0
Hyalinized (fibrosed) glomeruli	3.0	3.0	12.0	12.0
Normal glomeruli	96.6	96.6	0.5	0.5
		100.0		100.0
Hyalinization of afferent arterioles:				
+++	0		6.0	
++	0		4.0	
+	7.0		7.0	
0	93.0	100.0	83.0	100.0
Capsular thickening:				
+++	0		17.0	
++	5.0		7.0	
+	11.0		9.0	
0	84.0	100.0	67.0	100.0
Adhesions of glomerular tuft to capsule	4.0		9.0	
No adhesions	96.0	100.00	91.0	100.0

*252 glomeruli studied.

†203 glomeruli studied.

‡Not associated with axial thickening.

hibited an old ulcer in the first portion. Gross and microscopical examination of the brain revealed moderate atheromatous changes of the arteries and focal areas of encephalomalacia. The aorta and external iliac arteries exhibited moderate atheromatous changes.

The remaining right kidney weighed 200 gm. On gross section, the cortex was pale and measured approximately 7.0 mm. in thickness. The line of demarcation between the cortex and the medulla was poorly defined in contrast to the kidney removed 4 years previously, which, except for the cyst, had been essentially normal on gross examination.

Both kidneys were subjected to the same type of microscopical analysis. Sections from both organs stained with methyl-violet and iodine showed no amyloid; sections were also stained with hematoxylin and eosin, eosin and methylene blue and Mallory's aniline blue.

All the glomeruli in the available sections were individually studied. An attempt was made to evaluate the degree to which intercapillary thickening involved each glomerulus. The glomeruli that exhibited one to five or more large (20 to 120 microns in diameter), discrete, hyaline globular masses in addition to diffuse thickening of the axis with or without small irregular hyaline masses were considered to have a *severe* degree of intercapillary glomerulosclerosis. The *moderately severe* lesions were those in which the glomeruli contained small irregular hyaline masses (less than 20 microns in diameter) in the midst of diffuse thickening of the axis of the glomerulus. The *mild* lesions consisted of only a diffuse thickening of the axis of the glomerulus. The extent of the involvement was evaluated by determination of the percentage of glomeruli exhibiting the lesions described above. The percentage showing complete hyalinization and that revealing afferent arteriolar hyalinization, capsular thickening and capsular adhesions were also calculated (Table 2).

Observations and Discussion

Of the 252 glomeruli studied in the sections of the kidney removed four years before death, 8 (3 per cent) were so completely hyalinized that little can be said concerning the mechanism of the fibrosis. The remaining 244 glomeruli showed nothing that could be interpreted as intercapillary hyaline thickening except for a single hyaline mass in the periphery of one glomerular lobule (Fig. 1). It is generally agreed that such masses are specific for the histologic picture in the kidney in diabetes mellitus if they are also associated with additional axial manifestations of hyaline thickening. It is noteworthy that this single glomerulus containing the hyaline mass showed no other thickening of the glomerular axis.

This isolated glomerular lesion may have represented the onset of intercapillary glomerulosclerosis. This is unlikely since it would be reasonable to expect that in the kidney obtained at autopsy, in which the fully developed picture of intercapillary glomerulosclerosis was seen, some glomeruli involved by a mild or early process should have been found simulating the isolated lesion discovered in the earlier specimen. As pointed out below, it is striking that none of the glomeruli seen at autopsy showed this picture; wherever discrete hyaline masses were found they were always associated with thickening of other parts of the glomerular axis. Accordingly, we believe that the single lesion described above bears no relation to the intercapillary glomerulosclerosis that developed later. It probably represents the reparative process consequent to a variety of glomerular injuries not related to the diabetic state.

Of the 203 glomeruli studied in the kidney obtained at autopsy, 25 were so completely hyalinized that little can be said concerning the mechanism of the fibrosis. Only 1 glomerulus out of the remaining 178 was devoid of intercapillary thickening. Various degrees of this abnormality from severe to mild were found. Because of confusion in the literature regarding the various stages of this process,[9] we consider it indispensable to grade the degree of renal involvement according to the extent of the process in each glomerulus and the percentage of glomeruli so affected (Table 2) as some authors have attempted.[5-7] The lesions of severe degree were found in 47.5 per cent of the glomeruli (Fig. 2-4). An additional 40 per cent showed less severe lesions comprising moderately severe lesions in 25 per cent and mild lesions in 15 per cent.

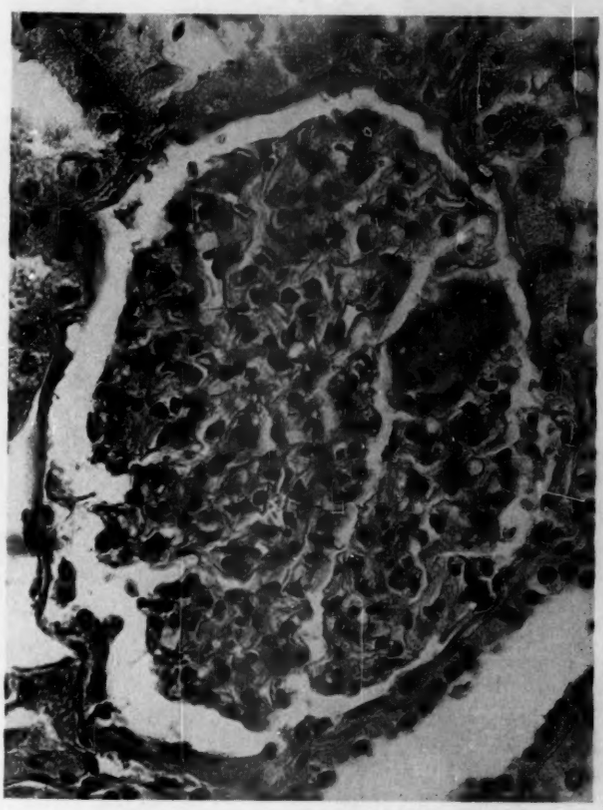

Figure 1. *Section of Kidney Removed Four Years before Death. A glomerulus with a single intercapillary hyaline mass (hematoxylin and eosin stain x 450).*

The relatively high percentage of the severe lesions in the kidney removed at autopsy represents an advanced stage in the development of intercapillary glomerulosclerosis and is considered consistent with the diagnosis of diabetes mellitus. Allen[10] has recently stated, "I am altogether convinced of the specificity of the nodular lesion," and

Bell[7] considers this lesion almost pathognomonic for diabetes. The mild lesions are considered by some authors as the forerunner of the nodular type, but their relation to diabetes has not been established.[9] The moderately severe lesions are believed

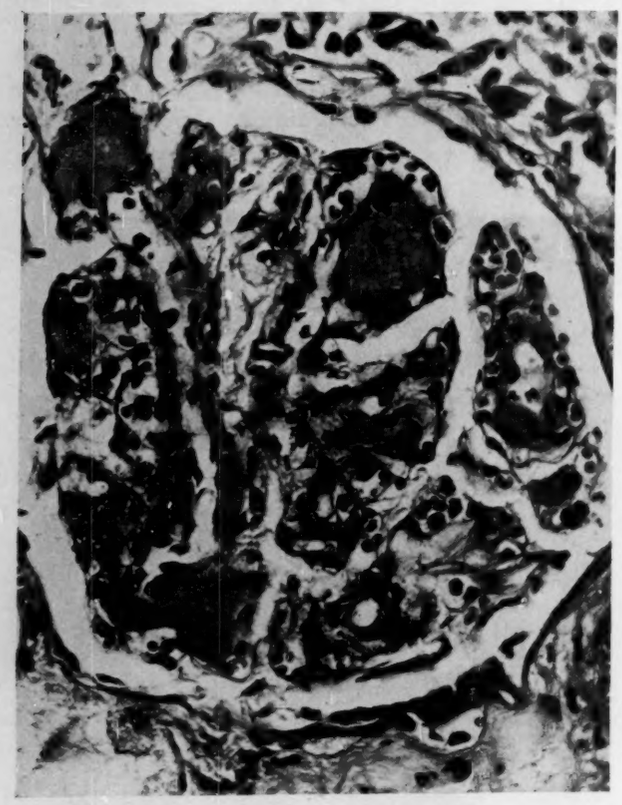

FIGURE 2. *Section of Kidney Removed at Autopsy.*
A glomerulus with intercapillary hyaline thickening and two large discrete hyaline masses (hematoxylin and eosin stain x 450).

to represent an intermediate stage in the development of the severe or nodular lesions.[8]

Other lesions such as afferent arteriolar hyalinization and glomerular capsular thickening and adhesions not generally considered an essential part of the picture of intercapillary glomerulosclerosis were present in the glomeruli of both kidneys. There was some increase in the incidence of these lesions in the four-year interval. Hyalinization of the afferent arterioles as seen in so-called benign nephrosclerosis increased from 7 to 17 per cent. The thickened glomerular capsules increased from 16 to 33 per cent. The incidence of adhesions of the glomerular tuft to the glomerular capsule, considered by many a concomitant of chronic glomerulonephritis, increased from 4 to 9 per cent. Because of the nonspecificity of hyalinized glomeruli their increase from 3 to 12 per cent cannot be considered of much help in evaluating the development of the lesions of intercapillary glomerulosclerosis.

The positive correlation between the severity of the renal lesions of intercapillary glomerulosclerosis and the degree of albuminuria has been emphasized by Henderson et al.[8] and others.[7, 9] Our patient showed no albuminuria during the four years prior to nor during the fourteen months following the nephrectomy in April, 1940. In July and August, 1941, during the period of severe sepsis and sulfathiazole treatment, all urine examinations revealed + to ++ tests for albumin (Table 1). In spite of recurrent sepsis and sulfadiazine therapy from September to November, 1941, albuminuria was absent. Repeated urine examinations until December, 1942, showed no albumin. Appearance and disappearance of albuminuria are consistent with an acute inflammatory process that healed. The possibility that the transient albuminuria was due to intercapillary glomerulosclerosis is unlikely because in the latter condition the albuminuria is constant and continuous once it appears. Thus,

FIGURE 3. *Section of Kidney Removed at Autopsy.*
A glomerulus with intercapillary hyaline thickening and small irregular and large discrete hyaline masses (hematoxylin and eosin stain x 450).

beginning in December, 1942, albuminuria recurred without any antecedent infection and continued in massive amounts until the patient died from renal insufficiency in August, 1944. In view of the large number of severe lesions of intercapillary glomerulo-

sclerosis found in the remaining kidney at autopsy, we believe that the correlation between these lesions and the massive continuous albuminuria is justifiable.

Intercapillary glomerulosclerosis, retinopathy and neuropathy are considered by many as degenerative concomitants of the diabetic state.[8-10] Henderson et al.[8] called attention to the close relation between advanced diabetic retinopathy and the severe lesions of intercapillary glomerulosclerosis.

In our patient the clinical evidence for degenerative phenomena associated with diabetes developed as follows: diabetes mellitus was first discovered in 1936 and was readily controlled by dietary regulation and moderate or small doses of insulin until 1941, when she was hospitalized for severe sepsis after high ligation of the saphenous veins. From the beginning of the ten-month period of hospitalization insulin was unnecessary until the terminal illness in 1944. Peripheral neuropathy developed in 1942 and improved slightly during the remainder of her life. Impairment of vision, first noted in 1942, progressed gradually until serious reduction of vision associated with advanced diabetic retinopathy was found in 1944.

It is noteworthy that in spite of the excellent control of the diabetic state, neuropathy, retinopathy and massive albuminuria developed six years after the discovery of diabetes mellitus and persisted to the eighth year, when the patient died from renal insufficiency. This observation is similar to those of other authors,[11, 12] one of whom stated that "the duration of diabetes mellitus rather than the method of treatment is the most important factor in the development of the degenerative changes."[10]

At no time, however, did our patient present the nephrotic syndrome, and renal insufficiency supervened only in her terminal illness. In this connection it is noteworthy that intercapillary glomerulosclerosis of as severe degree as was found in this patient is not necessarily associated with the nephrotic syndrome originally observed in the cases described by Kimmelstiel and Wilson.[1] The development of the nephrotic syndrome may be related to the duration of the severe intercapillary lesions before renal insufficiency occurs.

Of fundamental importance is the demonstration that our patient showed no pathological evidence of intercapillary glomerulosclerosis at the time of the nephrectomy although she had been suffering from diabetes and mild hypertension for four years, and yet at some time during the next four years degenerative phenomena in the peripheral nerves and eyes and also massive albuminuria supervened. Clinical evidence of the pathologic renal process did not appear until two years before death, in the sixth year of the diabetes, and at autopsy the fully developed picture of severe intercapillary glomerulosclerosis in the remaining kidney was evident.

On the basis of clinical observation on 43 patients Mann et al.[13] reported that the average duration of life after the appearance of signs of renal disease was six and four-tenth years (range two to twelve years). Our patient's rapid course may have been due to sepsis or the fact that she had only one kidney when the degenerative phenomena associated with diabetes mellitus developed, or to both.

Summary

A single kidney obtained at autopsy from a patient with diabetes mellitus of eight years' duration showed severe intercapillary sclerosis in 47.5 per cent of the glomeruli. The other kidney, removed four years earlier for a suspected neoplasm, showed no evidence of intercapillary glomerulosclerosis.

Six years after the onset of diabetes mellitus, neuropathy, retinopathy and massive albuminuria developed and persisted until the eighth year, when the patient died from renal insufficiency. At no time was the nephrotic syndrome present.

The lesions of intercapillary glomerulosclerosis definitely developed during the last four years of life and possibly only during the last two years

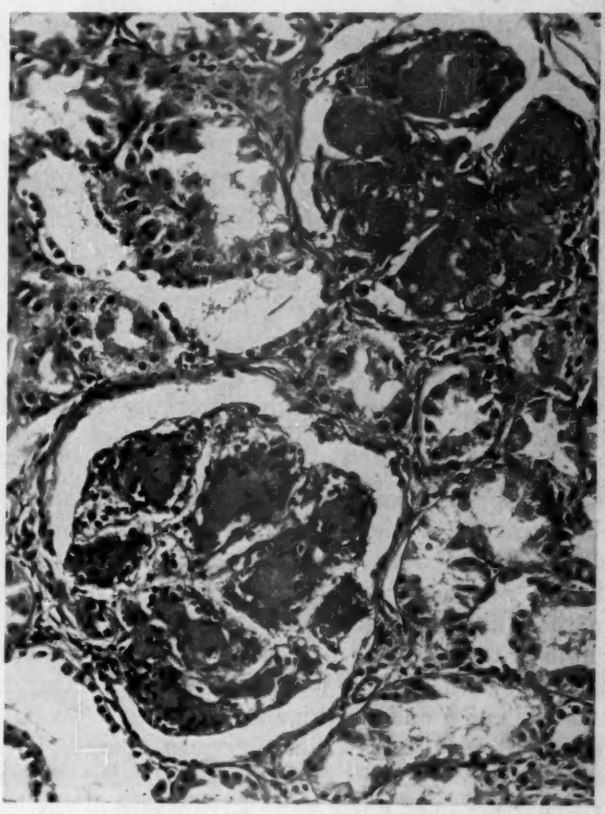

FIGURE 4. *Section of Kidney Removed at Autopsy. Two glomeruli with intercapillary thickening and multiple small irregular and large discrete hyaline masses (hematoxylin and eosin stain x 300).*

when the degenerative phenomena and massive albuminuria mentioned above were found.

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THE RELIABILITY OF THE MALE NORTH AMERICAN FROG (*RANA PIPIENS*) IN THE DIAGNOSIS OF PREGNANCY*

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WITHIN the past two years many reports summarized by Galli-Mainini[1] have appeared describing a new technic for diagnosis of pregnancy utilizing male amphibia. A great many species of frogs and toads have been described as useful for this procedure, and it is highly probable that many varieties of amphibia have equal value. At the present time two species have received the greatest attention. Galli-Mainini,[2] working in South America, has used a toad indigenous to that area—the *Bufo arenarum*. His recent report on the results of approximately 1000 tests using this amphibian indicates a high degree of accuracy, approximately 98 per cent, with no false-positive results, the 2 per cent errors being false-negative reactions. In the United States a widely indigenous frog, the common leopard frog known as the *Rana pipiens*, has been used for this work, chiefly by Wiltberger and Miller,[3, 4] and Robbins and Parker.[5] To date reports from these North American sources have been of a provisional type, and no extended clinical trial has yet been cited. The advantages of the use of male amphibia are so striking that the technic has created wide interest and possibly considerable use. It therefore seems both necessary and urgent to report results obtained to date with the use of the male frog. Only thus can it be determined whether the test is of sufficient sensitivity and specificity to merit further use.

The practical advantages of this technic are so striking that only a lack of accuracy could block its widespread adoption. In contrast to the five days required for the performance of an Aschheim-Zondek test on immature rats or the two days required by the female rabbit in the Friedman modification, the male-frog test requires at the most two hours.

The cost of male frogs is only a small fraction of that of rats or rabbits, and, moreover, the amphibia can be kept in small aquaria. From the standpoint of economy and ease in maintenance of a stock of available animals, the frogs are therefore vastly superior to these mammalia.

The only significant problem encountered to date in the use of these amphibia has been alluded to in an earlier report[6] — namely, the toxicity of many urines for them. At the time of the previous writing,[5] death of the frogs subsequent to their injection with 5 cc. of whole urine was a frequent occurrence. For totally obscure reasons, this problem has become much less bothersome at the present time, being no more common with male frogs than with other types of laboratory assay animals. However, it was because of this toxicity of urine that blood serum, containing fewer waste metabolites than urine, was suggested as a method of circumventing the problem.[6] Accordingly, 5 cc. of blood serum was substituted for urine in the performance of the test. Although on purely theoretic grounds serum should contain an adequate source of gonadotropic hormones during pregnancy, and although serum has been successfully substituted for urine in the performance of the Friedman test as well as others, it soon became apparent that serum was quite unsatisfactory for the *Rana pipiens* test. In a fairly large number of patients studied, proved subsequently to be pregnant, serum gave many false-negative results — about 15 to 20 per cent of the total series.[7] As a consequence, the substitution of serum in the performance of this technic has been dropped, and the present communication concerns itself only with an analysis of the results of the use of urine.

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Materials and Methods

Three hundred consecutive urine tests submitted to the laboratory of the Mallory Institute of Pathology of the Boston City Hospital for the diagnosis of possible pregnancy comprise this report. These tests represent all the varieties of diagnostic problems that may be encountered in any general-hospital laboratory, and, so far as possible, all the samples are consecutive. Hence the present report should reflect common clinical experience. As in any general pregnancy diagnostic work, the urine specimens submitted for hormonal assay fell into one of several fairly well defined clinical categories. For the most part these can be stated as possible normal pregnancy; possible ectopic pregnancy; possible fetal death or miscarriage, in which the problem of evaluating the viability of the gestation hinges on the hormone level in the urine; and a pelvic mass in which the differential diagnosis lies between intra-abdominal tumor and pregnancy or both. Almost all the 300 tests fell into one of these four groups. A few tests were performed after surgical removal of hydatidiform moles. Since each of these categories presents a somewhat different laboratory diagnostic problem, it seems advisable to study each group separately. Thus the performance of the frog test can be specifically evaluated in each category, undistorted by the good or bad results obtained in the others.

In each case the validity of the laboratory diagnosis was checked by a clinical follow-up study of the patient, for such time as was required to make certain the clinical status of the patient. In normal pregnancies, a clinical follow-up period of a few months usually sufficed. In the urine samples submitted from patients suspected of miscarrying, the exact status of the pregnancy at the time of performance of the test was frequently very difficult to ascertain. Many such tests were therefore discarded as being insufficiently clearcut from the clinical standpoint for inclusion. When possible, histologic study of curettage or surgical specimens was used to corroborate the clinical diagnosis. In a few cases parallel injections with rats or rabbits were employed as controls for the frog test. Whatever the method, in each test cited in the present series a careful evaluation of the validity of the test was finally achieved.

The technic for performance of the test is substantially identical with that reported in an earlier paper and is therefore described only briefly.[5] In essence, it consists in the injection of 5 cc. of first-morning urine into the dorsal lymph sac of adult male frogs. No preliminary treatment of the urine is required except for occasional crude filtration of grossly turbid specimens. Approximately half an hour after the injection microscopical examination of the cloacal fluid for sperm is begun, the hanging-drop technic being used. The reaction of the individual animal is followed for approximately two hours unless a positive reaction occurs earlier. As indicated before, to the best of our knowledge, no reaction ever begins after a two-hour interval. In general, positive reactions begin in thirty to forty-five minutes and persist for several hours, and in general they represent "all-or-none" responses. Rarely, an animal reacts with the release of only a few sperm. Our experience indicates that in a positive reaction many sperm may be found in any high-power field. The basis for so-called weakly positive reactions is obscure, but it is clear that they bear no apparent relation to the original titer of hormone injected, probably representing variations in the reactivity of the individual frog. All tests have been performed on adult male frogs run in pairs, the animals being obtained from local collectors. However, since the animals used are captured in the wild state and since estimation of age, to say nothing of sex, is difficult, it would be wise when possible to use 3 animals per test, simply to lower the mathematical probability of encountering all immature or superannuated animals on any given specimen of urine. Although this difficulty in selecting suitable animals may be of some theoretic significance, practically speaking our results indicate that it has not offered any real problem. For similar reasons it is probably good practice to open all "negative test" frogs simply to ascertain by inspection of the gonads that the animals used are male, the external features being insufficiently characteristic for most workers to separate definitely males from females.

Results

The results are presented and discussed under each of four headings cited above.

Possible Pregnancy

As mentioned earlier this category is meant to include patients who present themselves to the physician as possibly pregnant with a history of a missed menstrual period or some disturbance in the regularity of the menstrual cycle. A total of 242 urine tests fall into this group, with the following results: correct positive, 113; correct negative, 117; false positive, 1; and false negative, 11.

With relation to the correct-positive reactions, it is obvious that these tests merely indicate the presence of an apparently uncomplicated early pregnancy. It is well known that at the beginning of pregnancy the titers of gonadotropin are extremely low and only begin to rise to any appreciable level after approximately fifteen days of gestation. Since many urine samples are submitted for analysis after only one or two days of amenorrhea, some even before the first missed period, it did not seem justifiable to call these extremely early negative tests false negative. It was arbitrarily decided, therefore, that fifteen days after the first missed period was

the earliest date at which a negative test would be accepted as incorrect. Therefore any negative tests before this arbitrary time limit were not considered false negative. Admittedly, fifteen days of amenorrhea comprises a somewhat long wait before a diagnosis is attempted. However, performance of a test before this time involves a calculated risk. When such tests are negative, despite the presence of a viable early pregnancy, considerable clinical confusion invariably follows. If the problem involved in doing tests within the first two weeks of amenorrhea is appreciated, only positive results should be considered as having value. In this same regard 13 tests performed on specimens of urines from patients who were within fifteen days of the first missed period were correctly positive. In fact, 4 specimens were within the first four days after the first missed period. These results are of interest only so far as they indicate that the male frog will react to some early pregnancies, even as the immature rat and rabbit. The 117 correct-negative reactions comprise a mixed group of patients: 104 with simple amenorrhea, 4 with beginning menopause, and 9 with very early pregnancies that fell within the interval of the first two weeks of amenorrhea mentioned above.

False-negative results merit careful attention and are considered in Table 1.

It can be seen that the first 6 false-negative tests cited were performed on patients within the period of fifteen to twenty-one days of the first missed period. It is entirely possible that these urine samples represent pregnancies with poor production of gonadotropin, since it is well known that individual pregnancies vary greatly in the quantity of hormone excreted. Extreme instances have been cited in which no detectable gonadotropin could be demonstrated throughout a normal pregnancy. In support of the possibility that some of these false-negative tests were due to low-titer urines is the fact that in Case 2 the patient spontaneously miscarried at two and a half months of gestation, suggesting the likelihood of an abnormal conception or implantation. Tests indicated in Table 1 as numbers 7 to 10 were performed on specimens derived from patients in the third and fourth months of pregnancy. Hormone titers at this time while rapidly falling should nonetheless certainly be detectable. Tests No. 7 and 8 are samples of urine from the same patient, a curious case of undoubted abnormality. The case was thought to represent an intrauterine fetal death with missed abortion, since the size of the uterus never conformed to the calculated duration of the amenorrhea. Two male frog tests were negative, and yet five months later, at a calculated nine months of gestation, a small infant of approximately five months' fetal size was born alive and died within two days. Under these peculiar circumstances, whether the negative frog tests are justifiably considered as falsely negative is a controversial point. Other factors, such as deterioration of the hormone titer of the urine while the specimen is in transit by mail, contributed to the above so-called false-negative results.

TABLE 1. *False-Negative Reactions.*

Test No.	Patient	Age	Period of Amenorrhea at Time of Performance of Test	Clinical History
		yr.		
1	M. P. C.	22	18 days	Normal pregnancy
2	L. H.	34	21 days	Patient pregnant at time of test; miscarried 1 mo. later.
3	C. K.	—	16 days	Normal pregnancy
4	B. B.	24	21 days	Normal pregnancy; urine specimen received by mail after several days of nonrefrigeration.
5	B. S. B.	22	16 days	Normal pregnancy
6	I. K.	—	21 days	Normal pregnancy
7	E. P.	28	4 mo.	Patient said to be 9 months pregnant; delivered 5-mo. size infant, which lived 2 days.
8	E. P.	28	4 mo.	Repeat test on above patient
9	M. J.	26	3 mo.	Normal pregnancy; urine specimen received by mail.
10	M. D.	—	4 mo.	Normal pregnancy
11	T. F.	—	5 wk.	Normal pregnancy

The solitary false-positive result encountered in the entire series of 300 tests fell into this group of so-called early normal pregnancies. The patient was a thirty-eight-year-old woman entering the hospital with intense jaundice, apparently of the obstructive type, and associated amenorrhea of two months' duration. The urine specimen submitted for hormonal assay was intensely icteric, giving a positive result on male frogs. Subsequently the patient died, and autopsy demonstrated an obstructing stone in the common duct, bile stasis of the liver with early biliary cirrhosis and a terminal acute hemorrhagic pancreatic necrosis. No evidence of pregnancy could be found. Many speculations might be offered to explain this positive result. Suffice it to say that bile added to normal urine has no effect on the male frogs. Estrogens do not produce spermatic emission in these animals, and at the present time no good explanation exists for the effect of this type of urine on male frogs. For the

time being, therefore, we have avoided icteric urines and thus have not re-encountered this problem.

Possible Ectopic Pregnancy

This small group of urines (5 specimens) was derived from women all proved to have ectopic pregnancy by surgical exploration. In most, the presenting clinical features were those of lower abdominal pain and some pelvic mass associated with a disturbance of the regular menses. In the childbearing age ectopic pregnancy was considered as the probable diagnosis, and a urine sample was subsequently submitted for hormonal assay. In 3 cases correct-positive results were obtained, the periods of amenorrhea in the 2 known cases being one month and three months. In another case the urine was submitted before the patient had missed her first period, and the result was negative, as was fully anticipated. Such a result cannot justifiably be termed a false negative. In the last case the patient was three weeks overdue, the frog test was negative, and at laparotomy a tubal pregnancy was found. In the aggregate these results compare favorably with those obtained with the use of any other type of laboratory animal.

Possible Fetal Death

This group of tests is one of the most difficult to evaluate. Patients, most of whom are known to be pregnant, begin to have vaginal bleeding, and the question of the viability of the fetus arises. Urine assay remains the only technic presently available for determining viability. Since the exact time of fetal death is seldom, if ever, clear clinically, it is most difficult to ascertain with any surety the exact status of the pregnancy at the time of obtaining the urine sample for assay. Thus, of the many cases of this type tested at this laboratory most had to be discarded. Only cases in which the status of the fetus could be determined fairly certainly at the exact time of performance of the urine test were included in this series. Thus, the total number of acceptable specimens was 23. No incorrect results were encountered. There were 6 correct-positive tests in which it was possible to show that fetal death had not occurred prior to the test and 17 correct-negative tests in which unequivocal evidence, such as passage of placental tissue, indicated the certain death of the fetus. Admittedly, this category has little critical value in the evaluation of a test for pregnancy. The difficulty in judging the clinical course of the pregnancy is so great that when the pregnancy test and the clinical status fail to agree it may well be the clinical impression that is in error. Thus, so-called false results in this group have little real significance since they may simply represent misinterpretation of the clinical status at any given time.

Pelvic Mass

The last group of tests, as the heading indicates, is derived from patients having a large pelvic mass representing either a tumor or a pregnancy or both. Seventeen tests comprise the total, and all were received from patients with either uterine leiomyomas or ovarian cysts. No cases of concomitant pregnancy were encountered, and all the tests were correctly negative.

The remainder of the series of 300 tests here reported were made up of tests performed on patients being studied postoperatively after surgical removal of a hydatidiform mole. All these thirteen tests were negative and agreed with the clinical follow-up study of the patients, some for as long as two years.

Discussion

The results already cited for the various categories are summarized in Table 2. It can be seen that of the series of 300 urine tests performed incorrect results were encountered in 13. Thus, the over-all accuracy of this technic may be cited as approximately 96 per cent. One of the incorrect results was falsely positive, the remaining 12 being falsely negative. In terms of false-positive results, the most important consideration, the error was a third of 1 per cent. In addition, it is well to remember that this single false-positive test was encountered in the urine of a patient with intense obstructive jaundice, and although the ultimate basis for this false-positive reaction is still obscure, repetition of the incorrect result can be avoided simply by the rejection of all such icteric urine specimens. Of interest is the fact that an additional sample similar to the one described above was received recently, and although no diagnostic report was submitted, the urine gave a positive test on the male frogs. It was later determined that the patient was not pregnant, implying that the substance present in this icteric urine behaved like the substance present in the earlier, similar specimen. Further study of this problem is now in progress.

Table 2. *Results of Pregnancy Test.*

Actual Diagnosis	Correct-Positive Tests	Correct-Negative Tests	False-Negative Tests	False-Positive Tests
Possible pregnancy	113	117	11	1
Possible ectopic pregnancy	3	1	1	—
Possible fetal death	6	17	—	—
Pelvic mass	—	17	—	—
Hydatid moles (follow-up study)	—	13	—	—
Totals	122	165	12	1

This analysis indicates that the male frog test is a procedure of sufficient specificity and sensitivity to merit further use and investigation. Although the frog fails to achieve the accuracy of

the immature rat in the Aschheim–Zondek test, the many other advantages of the use of the frog seem to outweigh this small difference in sensitivity. In competent hands the Aschheim–Zondek test employing immature rats achieves an accuracy of close to 99 per cent, compared with the 96 per cent of the frog test. This difference in sensitivity is of some theoretic interest since repeated parallel assays of urine samples on rats and frogs indicate a complete identity of sensitivity to gonadotropins for the two types of animals. The theoretic basis, therefore, for this difference in accuracy between the rat and frog is totally obscure.

The results here reported are intended to serve as a progress report and possible stimulus to further modification and investigation of this technic. In this regard, we are privileged to include several suggestions, as yet unreported, that may well enhance the accuracy of this test to a point where it will compare favorably with all other technics.

Goodof,[8] having available an abundant source of vigorous frogs, submits all newly received animals to a screening injection of a minimal reacting dose of chorionic gonadotropic hormone. Frogs failing to respond to this dosage level are discarded. By this means females, poorly developed males and subreactive animals are eliminated, and only known reactors are then used for diagnostic work. More recently, Elrich, Albright and Brenner,[9] working with the male *Rana pipiens*, encountered a high percentage of toxic urines. To avoid this problem, dialysis of whole urine against slowly running cold tap water for an hour was employed, following similar technics by Heller et al.[10] After this treatment it was found that all urine specimens were completely nontoxic, and therefore 10 cc. of urine was employed as the routine injection dose, doubling the size of the previous dose. Heller and Chandler[10] have shown that no hormone titer is lost in this dialysis treatment, and, therefore, with the use of 10 cc. of urine the sensitivity of the frog test has been appreciably increased. To date no false results have been encountered by these workers. The increased dosage that dialysis permits may well bring the accuracy of the frog test up to the level of the Aschheim–Zondek procedure. Another method of handling toxic urines has been used recently.[11] It comprises the precipitation of the hormone by the use of a mixture of ether and 95 per cent alcohol. The precipitate obtained is dissolved in saline solution and injected. This method is said to permit the use of larger volumes of urine and thus to enhance the sensitivity of the test. Moreover, the simple use of 3 frogs for each urine assay may well enhance the accuracy of this technic by mathematically lowering the probability of encountering all nonreactive animals. What effect on the accuracy of the male-frog test these various modifications may have is as yet not known; however, they bear promise for the future.

Summary

Three hundred routine, essentially consecutive urine specimens have been submitted to pregnancy hormonal assay utilizing the male-frog (*Rana pipiens*) test.

An over-all accuracy of approximately 96 per cent has been achieved. A single false-positive test, now believed to be readily avoidable, and 12 false-negative reactions were encountered.

The analysis of the results indicates that most of the false-negative reactions were encountered in cases of normal pregnancy within the first month of amenorrhea. Yet several positive tests were obtained in other cases within the first four days of amenorrhea, indicating that the problem is not one alone of insensitivity of the frog to chorionic gonadotropin, but of varying hormone levels in individual pregnancies.

The results obtained appear to justify the continued use and study of this diagnostic technic. Several possible modifications having considerable promise are mentioned.

Since this paper was submitted for publication the technic for the performance of the test has been modified. Twenty cubic centimeters of urine per frog is precipitated with 4 vol. of 95 per cent alcohol. The sediment obtained by vacuum filtration is dissolved in saline solution and injected. The results appear to be somewhat superior to those obtained with whole urine.

We are indebted to Mrs. Phyllis B. Marshall and Miss Gloria E. Mannix for their technical assistance.

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FATAL PANCYTOPENIA FOLLOWING THE USE OF "MESANTOIN"*

Report of a Case

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NEWPORT, RHODE ISLAND

"MESANTOIN" (3 methyl-5, 5-ethylphenylhydantoin), a close chemical relative of dilantin has been used as an anticonvulsant in the treatment of grand-mal seizures since 1945. In 1946 Harrison, Johnson and Ayer[1] reported a case of fatal aplastic anemia following the use of "mesantoin" and tridione. Since that time several cases of pancytopenia following the use of "mesantoin" have been reported.[2, 3] The following case of fatal pancytopenia occurring after the use of "mesantoin" is presented to stimulate further investigation of the properties of this drug.

CASE REPORT

L. V. D., a 31-year-old veteran of World War II, entered the United States Naval Hospital, Newport, Rhode Island, on January 7, 1949, complaining of bleeding from the right nostril of 2 days' duration. The nostril had been packed by his physician, but bleeding continued. He was admitted to the ear, nose and throat service, where local treatment with silver nitrate, fibrin foam and two blood transfusions of 500 cc. each failed to stop the bleeding. On January 12 he was transferred to the medical service, where it was learned that he had been taking "mesantoin" and phenobarbital for 6 months prior to entry because of "epileptic attacks," which allegedly followed a skull fracture in 1944. He had continued to take "mesantoin" in a dosage of 0.1 gm. daily until January 6, and had taken none since.

There was no family history of bleeding abnormality, and he had no past history of joint pains, visceral pain or hemorrhagic tendencies. He had noted no hematuria, hematemesis or melena.

Physical examination on January 12 revealed a pale, thin man in no acute distress. The right nostril contained a large, dark clot from beneath which oozed bright-red blood. There was a linear depression of the skull in the left frontal area. There were numerous discrete petechial hemorrhages in the skin over the entire body varying from pin-point size to 3 mm. in diameter. The mucous membranes were pale, and the uvula was swollen and dark. There was no palpable lymphadenopathy, the lungs were clear, and the heart was normal to physical examination except for the tachycardia. The liver edge was just palpable beneath the right costal margin and the spleen could not be felt. Neurologic examination revealed no abnormalities.

The temperature was 101.2°F. by mouth, the pulse 120, and the respirations 20. The blood pressure was 125/80.

Examination of the blood disclosed a red-cell count of 3,350,000, with a hemoglobin of 9.8 gm. per 100 cc. The urine was normal, and smears for malaria were negative. The bleeding time was 2 minutes, the coagulation time 2½ minutes (Lee and White method), and the clot retraction was very poor. On the 5th hospital day the red-cell count was 2,130,000, with 6.23 gm. of hemoglobin, and the white-cell count 1850, with 86 per cent lymphocytes and 14 per cent neutrophils. The color index was 0.98, and a smear of the peripheral blood revealed anisocytosis, poikilocytosis and toxic granulation of the neutrophils. The prothrombin time (Quick quantitative method) was 15 seconds (control, 13 seconds), and the blood urea nitrogen 17.8 mg. per 100 cc. of whole blood. Sternal-marrow aspiration smears revealed an aplastic marrow with an average of 1 normoblast in six oil immersion fields. The icteric index was 10, the cephalin-flocculation reaction ++++, and the platelet count 36,000.

In spite of the measures outlined below the pancytopenia progressed, with a red-cell count of 1,880,000 and a white-cell count of 1400 on the 9th hospital day. On the 14th day (the day of death) the red-cell count was 1,910,000, the white-cell count 1000, and the platelet count 24,000.

The patient was treated with daily transfusions of whole blood, intramuscular injections of penicillin, liver extract and "pentnucleotide," intravenous administration of vitamin K, oral administration of vitamin C, folic acid and yellow bone marrow. After each blood transfusion his temperature rose, but there were no other manifestations of a transfusion reaction. A tourniquet test on January 13 yielded complete ecchymosis in the test area. This test was repeated on January 19, when only 10 pin-point petechiae were obtained in the test area. This change in response coincided with the clinical impression of improvement, although the laboratory findings gave an entirely different view, and his temperature remained elevated, spiking to 105°F. after each transfusion. On January 20 a chest x-ray film showed mottled pneumonic infiltration in the left mid-lung field. X-ray films of the long bones were normal. Penicillin was continued.

On the morning of January 22 the patient was found unconscious in bed. Respirations were labored, and the cardiac rate was 96, with distant heart sounds. Moist rales were audible scattered throughout both lung fields. He was placed in an oxygen tent, but respirations ceased shortly thereafter.

Post-mortem examination revealed petechial hemorrhages in the skin of the extremities, chest and abdomen. There was a large amount of dried blood in the nares and pharynx. Diffuse subpericardial and subpleural hemorrhages were present, as well as subserosal hemorrhages of the entire gastrointestinal tract. There were subcapsular hemorrhages of both kidneys, as well as submucosal hemorrhages of the pelves and ureters. Numerous large, poorly defined hemorrhagic areas were seen in both lungs, along with a moderate amount of pulmonary edema and carnification of the left lower lobe with pleural thickening. Examination of the brain showed several large subdural hemorrhages and large areas of cortical necrosis on the ventral aspects of the frontal and temporal lobes extending into the white matter. Many recent hemorrhages were present in the frontal, parietal and temporal cortex. The bone marrow was yellowish brown.

Microscopical examination disclosed terminal subendocardial and subepicardial hemorrhages, with early necrosis of the adjacent myocardium. There was moderate pulmonary edema, organizing lobar pneumonitis in sections from the left lower lobe and recent hemorrhage into the alveoli in many sections. Recent and older partially absorbed hemorrhages were present in the cerebral cortex and white matter, and advanced cortical necrosis was observed. The sternal-marrow blocks showed marked aplasia with increased fat, reticulum cells, a rare erythroblast and a rare myelocyte. No megakaryocytes were seen.

SUMMARY AND CONCLUSION

A case of fatal pancytopenia following the use of "mesantoin" and phenobarbital is presented. Autopsy revealed multiple visceral and cutaneous hemorrhages, an organizing lobar pneumonia and an aplastic bone marrow.

Accumulating evidence suggests that further investigation of the possible toxic properties of "mesantoin" is advisable.

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*The opinions and assertions contained herein are the ones of the authors and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

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MEDICAL PROGRESS

ACTIVE IMMUNIZATION

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DURING the past three years there have been many general and special contributions to the subject of active immunization. The principles and practices of pediatric immunization have been discussed in some detail by Miller,[1] who has long combined both practice and research in this field. The latest revision of the American Academy of Pediatrics *Handbook*[2] takes note of most of the recent revisions in immunization practices and provides, as always, many thought-provoking statements and opinions. Along a different train of thought, Parish[3] has presented a stimulating discussion of the present knowledge regarding both principles and practices of prophylactic inoculation, together with a consideration of probable future trends. Top,[4] as one of several participants in a symposium on immunization procedures,[4-8] has denoted the criteria that are helpful in assessing the value of an immunizing agent: safety, effectiveness, usefulness and ease of administration. His brief paper illustrates these principles, and considers their significance for both the health officer and the physician in private practice. A further item of usefulness for the practitioner is a pamphlet[9] recently issued by the United States Public Health Service, summarizing recommended immunization procedures prior to foreign travel.

Most of the problems underlying the principles of immunization remain little advanced as compared to the situation two or three years ago; in some fields, however, new information of significance has appeared. Freund,[10] in a scholarly review of certain aspects of this field, gives particular consideration to the cells responsible for antibody formation, and to the use of adjuvants for enhancement of the immunizing effect of an antigen. Several other lines of research are now being actively pursued by numerous investigators, and may lead within the next few years to significant advances in the understanding of the basic mechanisms that underlie immune phenomena. Meanwhile, it is of value to consider the advances of a somewhat more empirical nature that have taken place in the control by immunization of certain diseases of importance in the northeastern United States: diphtheria, influenza, pertussis, pneumonia, rabies, smallpox, tetanus, tuberculosis and typhoid fever. A previous review[11] considered all these diseases except pneumonia and tuberculosis, and also included scarlet fever. Little new information has appeared regarding immunization against the latter disease, except for a few studies using precipitated antigens,[12, 13] which show promise but require more extensive trial. The present review has of necessity included further consideration of many problems taken up in the 1946 review; space forbids the recapitulation of many developments that were previously considered, and reference is made to the earlier publication for such material when it relates to current findings.

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DIPHTHERIA

Recent Trends

Increase in adults. The wave of diphtheria that swept over most of Europe during the recent war has been well summarized by Stowman.[14] The possible effects of this epidemic on diphtheria trends in the United States have been considered in detail by several writers.[15-17] Whether many new and virulent strains were introduced into this country from Europe, or whether the increase of cases in recent years in the United States was due primarily to domestic factors, as Anderson believes,[16] there is no doubt that marked increases in both the incidence and the severity of diphtheria have been noted in various sections of this country. The rise began to be noticed about 1940, passing its maximum at different times in different localities. Nowhere in the United States were these increases at all comparable with the twentyfold increases observed during the height of the Norwegian and Dutch epidemics. Nevertheless, the fact that a threefold or fourfold increase should occur in a community such as Massachusetts, where extensive immunization programs have been carried out for many years, has called for a re-examination of the factors that determine susceptibility or resistance to diphtheria in the individual as well as in the herd.

One of the outstanding trends in the recent pandemic of diphtheria has been the marked increase in the percentage — and indeed often in the actual numbers — of adult cases. This has been noted in Massachusetts and has been reported from many widely separated areas — such as Minnesota,[18] California,[19] Utah,[20] France,[21] Italy,[22] Denmark[23] and Germany[24] — and in fact has been characteristic of the entire diphtheria picture in Europe.[14] This shift appears to have been due to two factors. The first is the obvious fact that, where immunization among children has been extensively carried out (as in Denmark, parts of France and many areas

of the United States), any increase in diphtheria will be likely to affect adults relatively more than children. For effective immunization in children should leave only a small proportion unprotected — perhaps 2 to 10 per cent — whereas the figures of Schick[25] and others indicate that at least 15 to 20 per cent of adults are Schick positive and therefore presumably susceptible to diphtheria. Moreover, the early observations of Park,[26] variously confirmed during the last twenty years, have shown that these figures are representative only for adults from urban or otherwise congested areas, far higher Schick-positive rates being found among many adult groups. Twenty-five years ago White,[27] in Massachusetts, found 73.5 per cent of country schoolteachers, 77 per cent of Smith College students and 35 per cent of all adults surveyed to be Schick positive.[27] A similar observation was made by Crooks in 1925.[28] It is true that some recent surveys have found no more than 24 to 30 per cent Schick-positive reactors among American military personnel,[29-32] and even lower rates have been noted elsewhere.[33-35] But numerous other reports disclose much higher Schick-positive rates among Americans — for example, 29 to 45 per cent in medical students,[36] 49 per cent and 70 per cent in student nurses,[37, 38] 40 per cent in prison inmates, and 51 per cent to 82 per cent in parents or teachers,[39, 40] 34 per cent in 18,000 Navy recruits[41] and 42 per cent in a smaller Navy group[42] and 44 per cent in 2983 Army personnel.[43] In other countries similar figures have appeared: from 42 to 87 per cent positive reactors among various adult groups in Canada[44-47]; 46 to 60 per cent among Australian medical and nursing students[48]; 51 per cent among English mothers[49]; and 67 per cent among Norwegian mothers.[50] Finally, diphtheria may occur under some conditions in persons who have immunity equivalent to the level of a negative Schick test; Ipsen[51] has reported a series of cases, observed during the wartime epidemic in Denmark, in which diphtheria occurred despite an immunity level far above the accepted minimum supposedly adequate for protection. Thus, it is necessary not only to revise established concepts regarding the general level of Schick positiveness in adults but also to re-emphasize the fact that a negative Schick test is not an infallible indication of immunity.

Efficacy of Immunization

One may ask at this point, What evidence is there that diphtheria immunization is actually effective? What have been the actual proved results following its use? Certain of the answers to this question, already summarized,[11] indicated that adequate immunization against diphtheria has given as much as 85 to 95 per cent protection. Several recent reports from widely scattered areas have supported these figures.[52-55] However, a few studies have not been so optimistic, showing only about a 50 per cent protection rate.[56-59] Practically all reports note that cases in the immunized, where they do occur, are relatively mild, with few or no deaths. In a Swedish series, for example, the death rate was 1.6 per cent (1 in 61) in inoculated compared to 11.7 per cent (24 in 267) among the uninoculated patients.[58] This is strikingly confirmed by Ipsen,[51] who observed 8.7 per cent deaths among 287 unvaccinated patients as against no deaths among 138 partially or completely vaccinated patients. Poulain[21] likewise reported 30 deaths in 490 unvaccinated, and no deaths in 90 vaccinated patients.

It has been noted previously[11] that some failures to achieve protection can be ascribed to a lack of understanding of how to use diphtheria toxoid — for example, the use of two doses of fluid toxoid or one dose of alum toxoid, or the administration of any kind of toxoid at one-week intervals. In other instances, failure may correctly be attributed to the use of toxoids of insufficient potency. Such instances have been detected by careful observers in England[60] and Denmark.[61] One wonders whether such a factor played a part in the severe outbreak reported by Fanning[62] in an English girls' school. Fifteen cases of diphtheria occurred among 299 previously immunized students, whereas 3 occurred among 23 unimmunized pupils. Although 96 per cent of the pupils had been immunized, only 69 per cent were Schick negative. However, several of the cases were in children who had just previously shown a negative Schick test.

In any attempt to evaluate the efficiency of diphtheria immunization, the rate at which immunity wanes must also be considered. It was previously noted[11] that anywhere from 3 to 20 per cent reversion to the Schick-positive state has been seen at the end of a year; these studies and others indicate that over a period of four or five years anywhere from 12 to 35 per cent relapses from immunity to susceptibility may be expected.[63-65]

In summary, then, it appears that from as little as 50 per cent to over 90 per cent protection may be expected from adequate diphtheria immunization, and that in any case the complication and mortality rate in immunized persons will be very low. However, it is unfortunate that few, if any, truly controlled studies on the results of diphtheria immunization have been carried out, so that the efficacy of this procedure cannot be assessed as precisely as, for example, that of influenza and pertussis immunization. To be sure, the incidence and severity of diphtheria in many immunized groups have been compared with rates in unimmunized subjects. However, there is little evidence in most such reports that the controls were of comparable economic status, hygienic habits, family size and so forth. Consequently, the claims for diphtheria immunization have been vulnerable to the attacks of the skeptics, among the most ingenious, persistent and

iconoclastic of whom is Rendu[66] in Lyon, France. According to Rendu, for example, although the immunization of school children in Geneva in the 1930's was followed by a decrease in diphtheria, there was also a comparable decrease in uninoculated areas, and the recrudescence of diphtheria in Geneva in 1941–1944 was as marked as it was in Neuchâtel, where no immunization program had been carried out. In another article, Rendu[67] undertakes to refute a series of French reports on the striking effect of toxoid in aborting diphtheria outbreaks in civilian and military personnel. In a recent paper he[68] dissects some of the data regarding diphtheria immunization in the French Army, particularly with reference to an extensive program for immunizing Schick-positive soldiers, which was claimed by Dopter[69] to have led to an eightfold reduction in the incidence of the disease among those immunized. These results were based on the premise that all soldiers developing diphtheria prior to completion of immunization should be classed as "unimmunized"; as would be expected, a large proportion of cases occurred in this group, since they were invariably new recruits. Rendu challenges this premise and shows that, if all such cases are classed as "immunized," there is no difference in the diphtheria incidence between "immunized" and "unimmunized" troops. Obviously, one cannot accept either Dopter's assumption (that Schick-positive, inoculated troops can be compared with Schick-negative, uninoculated troops) or the extraordinary concept of Rendu that, if a man is scheduled to be injected, he shall be classed as "immunized." Such fallacies weaken Rendu's strongest argument, which is that many items of "evidence" for the efficacy of toxoid are actually inconclusive. Nevertheless, his widespread statements that diphtheria toxoid is not only useless but also perhaps harmful have led in some quarters to a reluctance in accepting immunization. Poulain,[21] also of Lyon, analyzed the actual results of immunization in that city, and showed that, in each age group, the diphtheria rate in the immunized was about one tenth that in the uninoculated, and furthermore, that no deaths occurred in the immunized persons during the four years of an active immunization program. Furthermore, he presents evidence that, in the last fifteen months of this program alone, 22 deaths in unimmunized children might have been prevented, if about 15 per cent of the population had not ignored or evaded the city's immunization program, in part because of misinformation as indicated above.

Methods of Increasing the Effectiveness of Immunization

Three important approaches may be considered: addition of an adjuvant, increasing the dose, and giving more frequent or more numerous doses. It is well established, for example, that the addition of numerous substances (of which alum is merely the best known example) will increase the effectiveness of a given quantity of toxoid. Recent laboratory and clinical observations[70-74] give strong evidence that a similar effect is achieved by a mixture of toxoid with bacterial suspensions such as pertussis vaccine. Such measures may be of great value in establishing an adequate primary immunity. There is a growing recognition, however, as noted above, that primary immunity will wane sooner or later, and hence that it is necessary to administer "repeat" or "booster" doses at suitable intervals — as when a child first enters school. Numerous studies confirming the efficacy of such a procedure have previously been assembled,[11] but the optimum dose for this purpose has yet to be determined. Wishart et al.[75] gave various quantities of toxin or toxoid to eleven groups totaling 378 persons. They found that 4 flocculating (Lf) units (about 0.1 cc. of the usual toxoid) produced an antibody response in over 95 per cent of previously immunized subjects.

Reactions. However, even a 2-Lf dose caused local or general reactions in at least 15 per cent of adults.[75] In the United States Army, a comparable program elicited marked reactions in 9 to 10 per cent of the subjects injected.[43] In another United States Army group the incidence of reaction was apparently reduced by immunization of only the Schick-positive reactors, with graded doses of toxoid.[32] However, this is not always practical, and the incidence of reactions found in this study was much lower than that observed in other series. Boyd[76] attempted to screen a group of 131 British soldiers by testing with Schick toxin and diluted toxoid. The 98 subjects who were not sensitive to the diluted toxoid received 0.2 cc. of undiluted alum-precipitated toxoid; almost 40 per cent had severe local or general reactions. A similar experience is reported by Vollum and Wilson[77] in immunization of nurses. Thus, until a more suitable method for immunization of adults is developed, mass immunization of such groups will continue to present a problem. Another approach to elimination of reactions is to adopt a different route of administration. Masucci, Gold and de Falco[78] have tried Bousfield's[79] device, administering toxoid in the form of lozenges placed under the tongue. They observed no untoward reactions, and a good antibody response in previously immunized subjects, but no response in persons who had not previously received immunization; thus they confirmed Bousfield's original observations.

Most recent studies, however, have been directed toward the elimination of the reaction-producing substances in toxoid, which have generally been thought to be the bacterial proteins present in the crude preparation. Peshkin and Rapaport[80] employed a partially purified toxoid prepared by a calcium phosphate adsorption and elution method.[81] It is difficult to judge whether the severe reactions induced by their product were due to a failure to

achieve much purification, or to the unusually large amount of toxoid protein that they injected. Holt,[82, 83] of the Wright–Fleming Institute in London, has described a method of preparing a purified aluminum-phosphate-adsorbed toxoid of constant composition, which is relatively free from impurities and highly antigenic. Bousfield[84, 85] has reported very satisfactory results from its clinical use. Using a different approach Ross[86] has eliminated a large proportion of the nonbacillary toxoid protein by precipitation with protamine. Pillemer,[87] applying alcohol fractionation in the cold, has obtained a toxoid that is over 90 per cent pure. Levine et al.[88] have prepared toxoid of similar purity by ammonium sulfate fractionation. All these preparations have proved to be antigenic, and well tolerated in children,[84-86, 89] but such meager data as are available regarding their reactivity in adults indicate that reactions have not been entirely eliminated. The recent findings of Pappenheimer and Lawrence[90-92] may explain much of the difficulty that has been experienced in this respect. Using very highly purified reagents, they demonstrated, in careful quantitative animal studies, that toxoid protein and the other bacillary protein or proteins present in crude toxoid are both antigenic, but are immunologically distinct.[90] They showed that human subjects may be separately sensitive to either toxoid or bacterial protein, or to both, and that this sensitivity may be elicited by extremely small quantities of either substance.[91] In general, their subjects who had low antitoxin titers were relatively insensitive to the toxoid protein, whereas exquisite sensitivity to this fraction was rather common among immune subjects. Sensitivity to bacterial protein was not closely correlated with serum antitoxin levels, although it was in general more marked in immune subjects. Finally, Pappenheimer and Lawrence[92] have demonstrated that immunity can be produced without discomfort by employing normal doses of purified toxoid in hyposensitive subjects, and reduced doses in hypersensitive subjects. This clearcut demonstration that acute sensitivity can exist to toxoid protein may require extensive revision of present concepts of diphtheria immunization, particularly in adults. Whatever the final answer may be, it is probable that the use of purified toxoid will become essential, and it is also likely that some sort of control or sensitivity test will still be required in adults before even a purified toxoid can be administered with impunity.

Neonatal Immunization

It has long been recognized that the passive transfer of maternal immunity to the newborn infant interfered with neonatal immunization up to the time that such immunity is lost, toward the end of the first half year of life. Cooke[93] has recently confirmed this by administration of combined diphtheria-tetanus toxoid to 284 infants, demonstrating a good response to diphtheria toxoid in infants lacking maternally transferred antibodies to diphtheria, a relatively poor response in young infants inheriting passive immunity, and a uniformly good response to tetanus toxoid regardless of age, since there is no inherited immunity against tetanus toxoid. These results indicate that too much dependence should not be placed on neonatal immunization of infants against diphtheria. However, the use of an antigen potentiated by admixture with adjuvants or combined with other antigens, such as pertussis bacilli, may overcome the handicap inherent in neonatal antidiphtheric immunization. Bell[74] found that 201 infants under six months, who received alum-precipitated toxoid combined with pertussis vaccine, showed essentially the same Schick-negative rate a year later, as was found in 236 older infants given alum-precipitated toxoid alone, and di Sant' Agnese[94] has observed that the booster response in both age groups is equally good one year after primary immunization.

Influenza

Effectiveness of Immunization

Several comprehensive reviews on influenza[95] and in particular on vaccination against influenza[96, 97] have recently summarized the principal developments of the past few years in the control of this disease. As noted in previous reviews,[11, 95] the large-scale vaccination studies of 1943–1944 in Army personnel showed an influenza attack rate of 2.22 per cent in the vaccinated as against 7.11 per cent in the controls. A similar outbreak in an institution,[98] analyzed in a subsequent report,[99] showed attack rates of 1.9 per cent in the immunized and 12.4 per cent in the unimmunized — roughly a 6:1 protection rate. The next major outbreak, a Type B epidemic in 1945–1946, was studied on two college campuses in this country, where vaccinated Army personnel and unvaccinated Navy personnel were concurrently exposed. The protection rates observed in the two studies were 9:1[100] and 24:1.[101] Simultaneously, a Type B outbreak in England gave opportunity for observing the effects of vaccine in that country; protection rates ranging from 2:1 to 5:1 in different groups were observed.[102] On the basis of such observations as these, there appeared to be many valid indications for use of influenza vaccine, even though the apparently short duration of the immunity obtained and the slight but definite danger of reactions were fully recognized.[103] Vaccination was recommended for use in persons with histories of severe influenza; in groups where absenteeism would create significant problems; in crowded colleges and technical schools, and so forth.[103] Some clinicians emphasized the value of immunization for "the very large group of infants and children from several months of age

until later childhood where the need for decreasing the susceptibility to influenza by inoculation with influenza vaccine is indicated,"[104] and others called attention to the value of such immunization for the aged, in view of the well established evidence[105] that the mortality from influenza tends to be highest in this group. The major emphasis was laid on vaccination before anticipated epidemics, in view of the evidence that influenza A recurred fairly regularly on a cycle of two or three years, and influenza B at intervals of four to six years.[106] However, interepidemic outbreaks[107] and even isolated cases[108] have been reported, so that a justification existed for use of influenza vaccine in interepidemic periods. Accordingly, vaccination against influenza was widely practiced during the catarrhal seasons of 1945–1946 and 1946–1947, in children,[109] industrial groups,[110-112] schools and colleges[113-117] and the general population. The vaccine used was composed half of Type B (Lee strain), and half of Type A (equal parts of PR8 and Weiss strains). The results observed during the influenza A outbreak of February and March, 1947, were, to say the least, disappointing. Attack rates in one group were 54 per cent in the vaccinated compared to 49 per cent in the unvaccinated[114]; three other paired groups showed 7.19 per cent against 8.09 per cent,[115] 20.2 per cent against 27.8 per cent,[116] and 9.5 per cent in both groups.[117] It was readily demonstrated in these and other studies[118-120] that the virus strain responsible for this outbreak, now widely known as the FM-1 strain, was antigenically quite distinct from the standard Type A strains employed in the vaccine although it was definitely a variant of Type A. It appears likely that a similar or perhaps identical strain caused the 1946–1947 influenza outbreak in England,[121] during which three paired groups exhibited attack rates, in vaccinated and unvaccinated subjects respectively, of 11 per cent against 21 per cent, 11 per cent against 17 per cent, and 7.1 per cent against 8.3 per cent — surprisingly comparable to the rates simultaneously observed in the United States.

A few months after it was isolated, strain FM-1 was incorporated into the standard vaccine preparations, replacing the Weiss strain, which in turn had been included previously because it represented the common variant of its time. This sequence of periodic and unpredictable shifts in the antigenic pattern of influenza A virus has aroused some caution in evaluating the usefulness of vaccination. This attitude is reflected in the conservative conclusions of the 1947 report of the American Public Health Association study commission on influenza vaccination[97] and also in an editorial, which states, "One can only conclude that as yet influenza vaccination is in its experimental stage, and its widespread uncontrolled use as a routine measure does not seem justified."[122]

Factors Affecting the Efficacy of Influenza Vaccine

Numerous investigators have described antigenic variations in influenza A virus, and two strains were isolated during the 1943–1944 epidemic that were definitely variants from the standard "A" pattern.[123, 124] Such variations may become the major problem in making influenza immunization effective. The persistence of variant strains of Type A influenza during the winter of 1947–1948 has provided opportunity to assess the value of the FM-1 strain in the currently available vaccine. The results are hard to evaluate. Meiklejohn and Bruyn[125] found essentially no antibody response to a locally isolated variant strain, in the serums of persons immunized with vaccine containing the FM-1 strain. On the other hand, Salk and Suriano[126] observed a definite reduction in the incidence of acute respiratory illness in persons receiving the "new" vaccine as compared with a control group receiving the "old" vaccine. Meanwhile, the possibility that further strain variants will arise is constantly present, and it is in large part for this reason that "listening posts" for early detection of new strains or new outbreaks of influenza have been set up on a nationwide and world-wide basis.[127] However, it has been pointed out[114] that the antigenic range of protection achieved by immunization might be broadened if the average antibody titer induced by the vaccine could be increased, since a rise in the titer to the homologous strain usually carries with it a comparable rise in the titers against related strains. Several possible methods of achieving the increase in titer have been explored. The simplest appears to be to concentrate the virus antigen. This has been effectively accomplished by centrifugation[128] and by alcohol precipitation,[129] both methods being designed primarily for purification, but yielding high concentrations of virus elementary bodies. It is indeed possible to increase the antibody response by increasing the dose of antigen,[130] but the gain is small in proportion to the stimulus applied, several workers having reported that a tenfold increase in the amount of antigen used gives an increase of only about two to two and a half times in antibody rise obtained.[131-133]

Repeated inoculations of vaccine would ordinarily be expected to raise the antibody level above that obtained with one injection, were the response to influenza vaccine similar to that observed with diphtheria and tetanus toxoids and most other antigens. Although such increases in antibody titer have been observed in swine after repeat injections of swine influenza vaccine,[134] this has not been borne out in human experiments.[132, 135, 136] The extensive studies of Beard and his associates[137] in swine, however, suggest that the difference between success and failure may depend upon the interval between doses.

Various adjuvants have been employed in efforts to potentiate the effect of a given quantity of influenza virus vaccine. The use of protamine has been suggested[138] and tried with but indifferent success.[132] Alum adsorption did not produce a gain.[139, 140] Results of procedures employing calcium phosphate as an adsorbent[141] have been inconsistent[133] but on the whole promising.[142] The most striking effects have been observed after the use of water-in-oil emulsions after the method of Freund.[143] Influenza virus emulsions of this type have proved to be highly antigenic both in animals[144] and in man.[132] The relatively high incidence of abscess formation induced by this method, however, is a drawback that has not at present been overcome.

Other Immunization Routes

Intracutaneous vaccination with one or two doses of 0.1 cc. of influenza vaccine has been tried, with results superior to those obtained with the standard subcutaneous route employed simultaneously in a control group.[145] Moreover, local and systemic reactions following the intracutaneous vaccine were markedly fewer than those with subcutaneous vaccination. Weller, Cheever and Enders[146] have likewise obtained adequate antibody responses after intracutaneous vaccination. In view of the fact that influenza vaccination is probably in most instances actually a booster procedure,[147] and that intracutaneous immunization is in general highly effective as a booster agent in many conditions, there appears to be a strong case for use of this route as a general procedure.

Since the earliest studies on the virus of influenza, efforts have been made to immunize human beings by inhalation of active or inactive virus. The logic of such an approach is fortified by the finding that influenza virus combines directly with cells of the respiratory tract in a specific manner analogous to the well known reaction of the virus with erythrocytes.[148] The broad pathogenic significance of this reaction has recently been illuminatingly reviewed by Burnet.[149] A series of experimental studies by Australian workers, using the inhalatory route, showed that some immunity could be produced by influenza virus adsorbed in this fashion, but the results were not decisive.[150-153] Francis and his co-workers[154] found that experimental infection with type B virus did not give staunch protection four months later and noted elsewhere that the results obtained by this method were inferior to those obtained with subcutaneous vaccination.[155] Henle and his associates[156] have made essentially similar observations. On the other hand, McLean and his co-workers[157] have observed a striking contrast in the antibody response induced in swine by experimental infection, as compared to parenteral vaccination. Comparable groups of swine were infected, and compared with groups given one, two or three doses of formalinized virus vaccine. An arbitrary scale was devised to measure the presence and severity of the infection induced by subsequent intranasal challenge with active virus. This scale gave a "morbidity score" of 88.6 in nonimmune unvaccinated control animals. The morbidity score for all vaccinated animals averaged 58.9, whereas animals recently recovered from a primary infection experienced a morbidity score of only 16.7. These results suggest that, at least in swine, the protection achieved for a short period by infection far exceeds that induced by use of vaccine. Whether these findings can be translated into human protection remains to be seen; certainly, one must acknowledge the possibility that immunization by the respiratory route has potentialities greater than those of the parenteral route. However, immunity resulting from infection is still type specific; experiments in ferrets have shown that recent recovery from influenza A does not in any way increase resistance to influenza B, and vice versa.[158]

Reactions

The widespread use of influenza vaccine during the past two years has provided extensive evidence that untoward reactions to the vaccine are not infrequent and can be particularly severe in children. Reactions have varied from local tenderness and swelling to severe, almost explosive (but transitory) febrile responses resembling influenza itself. The mechanism of these reactions is not wholly clear. Influenza virus has been shown to be toxic for animals,[159-161] but this toxicity disappears with inactivation of the virus, such as in the standard preparation of vaccine. Yet the particular severity of the reactions in children[142, 162-164] suggests that a toxic factor is involved. As pointed out by Dingle[95] and Salk,[165] the reactions in human beings may be due to a combination of both toxic and sensitization factors. Whatever their cause, they have been sufficiently frequent and severe to stimulate reconsideration of the customary dosage employed.[142, 162-164] In comparisons of the reactions induced by different vaccine preparations, it appeared that reactions to calcium-phosphate-adsorbed vaccine[142] or protamine-precipitated vaccine[112] were apparently milder than those induced by the standard red-cell eluate vaccine. However, such differences may have been due merely to differences in the inherent potencies of the vaccines.[166] Salk,[165] in an extensive study, found a very close correlation between the amount of virus injected and the severity of reaction produced. He concludes that, since increases in amounts of antigen used do not yield corresponding increases in antibody titers, the optimum dose of influenza virus should be no greater than that which will be reasonably well tolerated. This suggestion admittedly rests on the assumption that antibody titers and resistance to clinical influenza infection

are generally closely correlated. It conflicts with the findings of Hare et al.,[167] who concluded that the antibody response was inadequate after anything less than a full dose of vaccine.

Considerable alarm has been expressed over the danger of true allergic reactions from inoculation of influenza vaccine, which is derived from the chorioallantoic fluid of the infected chick embryo. Two fatal reactions are reported to have occurred, in both of which a history of sensitivity to eggs was later traced. The apparently alarming possibilities inherent in the administration of egg proteins to a large number of human beings were reviewed by Ratner and Untracht,[168] who collected evidence suggesting that the problem was a widespread one. The report by Curphey[169] of a death — said to have been allergic in nature — in a small child a few hours after an injection of influenza vaccine, and a similar report elsewhere[170] provided a basis for renewed caution in administering the vaccine. It is generally agreed that a history of possible sensitivity to egg protein should be carefully sought for; however, it is on record[171] that many injections of vaccine have been given, without reaction, to persons with histories of mild egg sensitivity. A recent editorial[172] has restated the widespread opinion that the risk of this type of reaction — slight as it is — might be reduced by further purification of the virus by the centrifuge[128] or alcohol[129] methods, thus eliminating most of the extraneous egg protein. However, a re-examination of the death reported by Curphey[169] suggests — as Salk[173] has pointed out — that it was due to a toxic rather than an allergic reaction. If such toxic deaths can indeed occur, the use of purified vaccines must be tempered with a caution against employing excessive quantities of virus, since the incidence of reactions rises sharply within a relatively narrow range of increase in virus concentration.[165]

(To be continued)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

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CASE 35271

PRESENTATION OF CASE

A forty-nine-year-old male cook was admitted to the hospital because of weakness, cough, chills and chest pain.

Six days before admission the patient noticed excessive fatigue. On the following day he developed anorexia, headache, dryness of the mouth, a light cough productive of whitish sputum with brownish streaks, and pain in the right anterior chest made worse by breathing. Four days before admission he had several shaking chills and the next day fatigue increased markedly. He developed pleuritic pains in the left anterior chest and had profuse sweats after ingestion of "red pills" that had been suggested by a druggist. Two days before admission the chest pain diminished, but over the following two days the cough became much worse, and since the day before admission the sputum had been streaked with red blood.

At twelve years of age he had had rheumatic fever and had been kept in bed for seventeen days. At twenty-one he had recurrent joint involvement after an upper respiratory infection. After he had recovered he had a tonsillectomy. For the past eighteen years his hip joints had bothered him intermittently, especially with weather changes. Sixteen months before admission he had seen several physicians because of easy fatigability, exertional dyspnea and occasional dyspnea at rest, and a slight cough. He was given digitalis and advised to reduce his activities. Two months later he was admitted to another hospital, where x-ray examination revealed an enlarged heart. He was advised to rest and to continue taking digitalis. He had never had ankle edema and no definite orthopnea. He had had gonorrhea five times between fourteen and twenty-four years before admission. On each occasion he was promptly treated and cured.

Physical examination revealed a well developed, well nourished, dyspneic man who appeared feverish and flushed. The skin was hot and moist. The tongue was coated and dry, and the throat red. The chest appeared normal, with good expansion. There were crackling rales, diminished breath sounds, and slight dullness to percussion in the right infrascapular area and over the right base posteriorly. The heart showed completely irregular rhythm with an apical rate of 104 and a radial pulse of 92. There were a Grade II apical systolic murmur and an apical mid-diastolic rumble. The left border of the heart appeared in normal position. The extremities were normal.

The temperature was 105°F., and the respirations 30. The blood pressure was 135 systolic, 55 diastolic.

Examination of the blood showed a red-cell count of 4,600,000 and a white-cell count of 6400, with

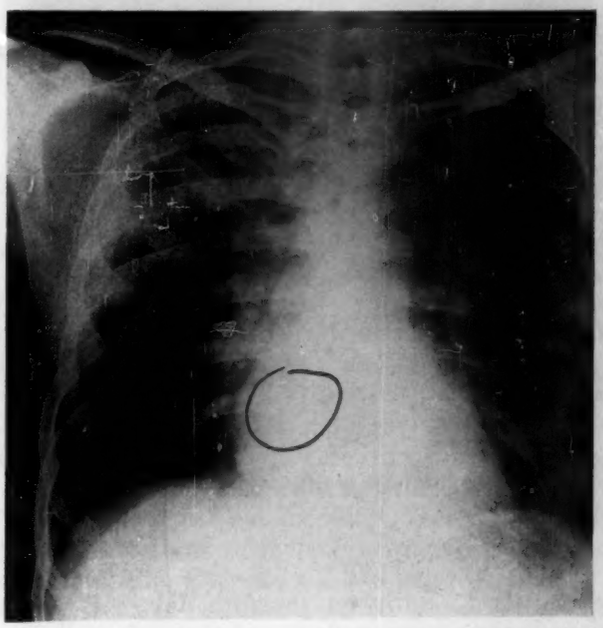

FIGURE 1.

89 per cent neutrophils, 7 per cent lymphocytes and 4 per cent monocytes. The urinary sediment contained 2 to 5 red cells and 4 to 6 white cells per high-power field and occasional granular casts. A stool was normal. Sputum smears showed a few gram-positive streptococci. Repeated smears were negative for tubercle bacilli. The sputum culture showed no pneumococci.

An x-ray film of the chest (Fig. 1) showed mottled increased density occupying the whole upper half of the right-lung field and appearing to include only the right upper lobe. The hilar markings were slightly increased. The heart was prominent in the region of the left auricle, and there was a prominence of the pulmonary artery.

The temperature continued at 103 to 104°F., and the respirations slowly rose over three days to a rate of 50. He was continued on digitalis and penicillin until the fourth day, when sulfadiazine was substituted for penicillin. A roentgenogram on the third day showed extension of the density to the right lower lobe and also involvement of the left lung (Fig. 2). On the fourth day the respirations became more labored and rapid, and cyanosis and dyspnea increased. The lungs filled with coarse rhonchi, and large amounts of bright-red sputum

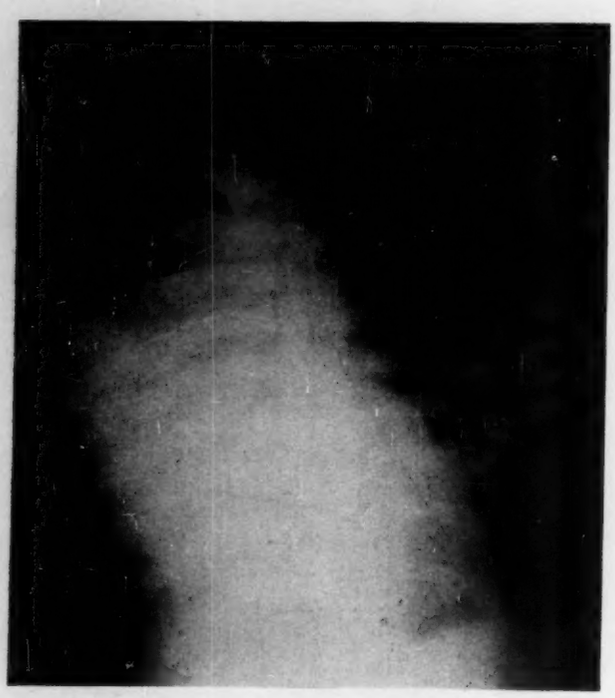

FIGURE 2.

were raised. Early on the fifth day the respirations became very shallow, and the patient died.

DIFFERENTIAL DIAGNOSIS

DR. ALLEN G. BRAILEY: I should like to see the x-ray films.

DR. MILFORD D. SCHULZ: This first film was taken prior to the illness; it antedates it by three months and shows normal lungs. The heart is enlarged in the region of the left auricle. Films made at the time of hospital entry show a mottled area of increased density occupying the major portion of the right upper lobe that in two days extended to the lower right chest, and there is also involvement of the left chest. The mottling has become quite confluent. The lung roots are larger on the films made at the time of the illness than before, but at no time is there evidence of fluid in either pleural sinus.

DR. BRAILEY: Would you make a diagnosis of rapidly advancing pneumonia from that picture?

DR. SCHULZ: Yes; or pulmonary edema. If one saw the last film only, one would be tempted to think that it was pulmonary edema, especially in the face of the mitral disease.

DR. BRAILEY: The significant features of this history are that a middle-aged cook with long-standing rheumatic heart disease died after eleven days of an acute febrile illness with symptoms largely confined to his chest. The causes of death that need to be seriously considered are: acute fulminating tuberculosis, pneumonia of some type—perhaps embolic — and acute rheumatic infection. The bloodspitting and the x-ray appearance of his lungs make it desirable to mention tumor and bronchiectasis also, but these seem to be excluded by the acute febrile course. Certainly, if present, they must have been complicated by severe secondary infection.

It is obvious from the protocol that tuberculosis was seriously considered by the medical service. However, very rarely does tuberculosis, even in an explosive, pneumonic form, kill in so short a time. On the other hand, it might be argued that this man had a seriously damaged heart, which served to hasten his death. It is reported that repeated smears of sputum failed to show tubercle bacilli. This is a major point against the diagnosis but does not rule out the possibility. This man had had symptoms referable to his heart for many years, and he must have had previous x-ray examinations of his chest. Yet there is no mention that tuberculous lesions had ever been observed prior to his present illness. It is very unusual for tuberculosis to arise *de novo* in a man of forty-nine who has shown no x-ray evidence of previous infection. I cannot exclude tuberculosis, but I very much doubt if that will prove to be the anatomical diagnosis.

The diagnosis of pneumonia is not so easily disposed of. It is obvious that he had a pneumonic process of some kind in his chest, and his whole physical course is not inconsistent with pneumonia due to pneumococci or one of the other pyogenic organisms. The polymorphonuclear percentage is increased, and the low total white-cell count may only be a commentary on the severity of his infection. However, one should have no particular difficulty in finding and isolating the offending organism in pyogenic pneumonia, whereas we are told that pneumococci could not be grown from the sputum and only a few gram-positive streptococci were seen. Furthermore, most of the organisms that may provoke a fatal pneumonia are quite susceptible to adequate treatment with penicillin or sulfadiazine. Yet these agents were of no value to this patient. There are forms of pneumonia, very exotic in this locality, that could have produced this picture — such as melioidosis and pneumonias due to some of the rickettsias and coccidiomyces. However, these conditions are so rare

in New England as to deserve hardly more than passing mention.

His cough, his marked bloodspitting and his increasing dyspnea and cyanosis are all consistent enough with repeated pulmonary infarctions. But if he had a shower of pulmonary emboli, where did it come from? We are given no hint of phlebitis of any peripheral veins, although we know from sad experience that the source of emboli is often not recognized during life. His auricles were fibrillating, and the formation of thrombi in the auricles is a fairly common and dreaded complication of such fibrillation. It is quite possible that he developed a thrombus of the right auricle or appendage, which then shed emboli from time to time to plug branches of the pulmonary arteries. But it would be very remarkable, indeed, if these emboli all elected to lodge in the artery to the right upper lobe as the x-ray report suggests. And what about his fever? I think pulmonary infarction would scarcely give rise to temperatures of 103, and certainly not to 105°F., unless the emboli involved were infected. But septic emboli from the heart imply an acute bacterial endocarditis involving the tricuspid valve, and of such a rare lesion we have no hint. I cannot exclude the possibility, but I doubt if this man died of pulmonary embolism.

Finally, there exists the possibility that this man died of acute rheumatic fever and its complications. The literature contains a number of contributions purporting to show that rheumatic infection may, of itself, produce a pneumonitis distinguishable from other forms of pneumonia and from chronic passive congestion. There is as yet no general agreement that such an entity exists, but neither can the evidence be brushed easily aside. Those interested in the subject may well begin with a scholarly paper by J. R. Paul[1] and a more recent review by Seldin et al.[2] These, and other authors, point to a group of patients with a history of manifest rheumatic infection who are struck down with an illness of sudden onset, a temperature often of high level, a hacking cough, bloody sputum, marked dyspnea and cyanosis and usually a fatal outcome within ten to fourteen days. Onset with chills is rare. There may be transient pleurisy; physical signs of lung involvement are often minimal. The white-cell count is usually high (as it was not in the subject of this discussion). X-ray study may show involvement of one or of several lobes. Often, there is little to distinguish the x-ray picture from that of chronic passive congestion. Study of the sputum reveals no significant organisms and usually little pus. Frequently, the evidence of cardiac failure, as in our present case, is not impressive. The venous pressure and circulation time may be very little elevated, and the pulse rate and blood pressure may be well maintained. At post-mortem examination, the outstanding features appear to be the mononuclear and frankly hemorrhagic character of the alveolar exudate, and attention is also called to a hyaline membrane lining the smaller bronchioles.

Whether these are features worthy to identify a separate clinical entity must lie outside this discussion. But it must be conceded that there are persons with a long-standing history of rheumatic infection who die as this man died — after a brief but stormy illness characterized by fever, cough, hemoptysis, rapidly increasing dyspnea, orthopnea and cyanosis with little evidence of heart failure but with evidence of a pneumonic process for which there is no readily apparent cause.

Clinical Diagnoses

Pneumonia, fulminating, ? etiology.
Rheumatic heart disease, with mitral stenosis.

Dr. Brailey's Diagnoses

Rheumatic heart disease, with mitral stenosis and auricular fibrillation.
Acute rheumatic fever.
Rheumatic pneumonia?

Anatomical Diagnoses

Atypical viral pneumonia, fulminating.
Rheumatic heart disease, with mitral stenosis.

Pathological Discussion

Dr. Benjamin Castleman: Autopsy showed rheumatic heart disease involving both the aortic and mitral valves, with a moderate degree of stenosis of the mitral valve. There was no evidence of superimposed bacterial endocarditis or of acute rheumatic endocarditis. The lungs were the interesting feature of this case. They were tremendous in size, the right lung weighing 2000 and the left, 1300 gm. Whenever one sees a lung weighing 2000 gm. the first thing to think of is lobar pneumonia. On the other hand this did not look like lobar pneumonia. The cut surface revealed a spotty granularity and was extremely hemorrhagic. The right upper lobe was entirely consolidated, and the middle and lower lobes to a lesser degree. In the left lung the process was limited to a large area near the hilus involving a third to a half of each lobe. We cultured them and were unable to get any pneumococci or streptococci. We thought immediately of the fulminating influenza-virus pneumonia or rheumatic pneumonia.

Microscopical sections showed fairly acute pneumonia, bronchitis and interstitial pneumonitis, a condition that has been described in atypical viral pneumonia.[3,4] There was infiltration of the alveolar walls as well as the alveoli themselves, more particularly around the bronchi, with polymorphonuclear leukocytes, fibrin and monocytes. The bronchioles were filled with organizing exudate. The atria and a large number of the alveoli were filled with blood, which was probably a secondary manifestation. The picture closely resembles sec-

tions that I found in our files of the old influenza epidemic of 1918, where the lungs were hemorrhagic and wet as these were. It is one of the few cases of atypical viral pneumonia that we have seen. Unfortunately, we did not have viral studies done on the material, so that we do not have actual proof of the diagnosis. There was 500 cc. of fluid in the right pleural cavity at the time of autopsy, and a little under 100 cc. on the left side.

DR. BRAILEY: Were there any Aschoff bodies in the heart?

DR. CASTLEMAN: No. We did consider rheumatic pneumonia, since this patient had a history of rheumatic infection. In rheumatic pneumonia as a rule one does not see so much cellular reaction, but rather a great many phagocytes and red cells. Also, the bronchi are usually not filled as these were. Of course, the whole question of rheumatic pneumonia is still a moot subject.

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CASE 35272

PRESENTATION OF CASE

A sixty-two-year-old man, a wool spinner, entered the hospital because of hemoptysis.

For many years the patient had had "bronchial trouble," with cough, gradually increasing dyspnea and occasional blood-streaked sputum for three years. Two and a half years prior to admission an x-ray film revealed a shadow in the left upper lobe, and hospitalization for further study was advised. Instead he resorted to "heat treatments," with some improvement. Three months prior to admission an x-ray film taken in the course of a mass survey confirmed the findings on the previous examination, and a bronchoscopy was performed, with some alleviation of the cough but with aggravation of the hemoptysis. On bronchoscopy the trachea was deviated slightly to the right, as if from extrinsic pressure on the left side; the carina was in the midline, with no widening or fixation. The orifice of the left upper lobe, visualized through the right-angle telescopic lens, appeared to be completely occluded by a rounded, smooth mass, which seemed to be in two lobules. No air was seen to be passing in or out of the orifice. There was some reddening of the left main bronchus and left-lower-lobe bronchus. Following bronchoscopy the patient was scheduled for hospitalization.

On physical examination diminished tactile fremitus was present over the left upper lobe posteriorly, and occasional rales were heard over this area. The heart was not enlarged. The liver edge was palpable two fingerbreadths below the costal margin. The prostate was enlarged to three times the normal size and was "rubbery."

The blood pressure was 180 systolic, 120 diastolic.

Examination of the blood showed 12.5 gm. of hemoglobin, with a white-cell count of 20,000. The specific gravity of the urine was 1.020; no albumin, sugar or acetone was present. The serum protein was 7 gm., and the nonprotein nitrogen was 36 mg. per 100 cc. The prothrombin time was normal. An x-ray film of the chest, with fluoroscopy and a barium swallow, showed elevation of the left hilus, with some increased density of the left apex medially. There was a 1-cm., rounded area of density in the left first interspace anteriorly. The left upper lobe was decreased about a third in size (Fig. 1). Elsewhere, the lung fields appeared clear. There was no evidence of pleural fluid. The esophagus was slightly deviated to the left at the level of the suprasternal notch. Just above this area there appeared to be slight compression of the trachea from the right; it was likewise slightly deviated to the left.

On the fourth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. HELEN S. PITTMAN: I hope Dr. Hanelin is going to help me on this x-ray report. It confuses me. I wonder if we may see the films now.

DR. JOSEPH HANELIN: These are spot films that show a part of the esophagus and also show the trachea quite well. I do not believe that the course of the esophagus, above the aortic arch, is particularly unusual. All the films of the chest were taken at the same time, or a day apart. I think the finding of greatest importance is evidence of collapse of the left upper lobe. The left hilus is elevated. There is diffuse increased density in the region of the apex, and there is an irregular area of density, about 1 cm. in size, in the left first interspace. The esophagus and the trachea below the level of the arch are only questionably abnormal. It is possible that there is a greater degree of indentation along the left aspects of these structures, but I cannot be sure of it. The lungs elsewhere are clear. The heart is not enlarged. The aorta is elongated and tortuous.

DR. PITTMAN: Is there any special compression of the trachea from the right?

DR. HANELIN: The trachea follows a somewhat tortuous course. If this were to result from extrinsic pressure, the adjacent mass would be of most unusual contour.

DR. PITTMAN: Then I am going to forget about it; because I do not know anything else to do about it that makes any sense.

The points that seem to me of interest and importance in this history are that this man, who had had cough, increasing dyspnea and occasional blood-streaked sputum for years and who had an intrabronchial mass, gave no history of ever having had a wheeze. He must have had a wheeze. There had apparently been no change over a period of two

and a quarter years. Two and a half years before admission, an x-ray film showed a shadow in the left upper lobe, and three months prior to admission a survey film confirmed the findings of the previous examination. That is of extreme importance. Apparently, there was no change over something more than two years. The right-angle telescopic lens was used in the upper lobes, and all we have is a visual report. So we do not know whether the mass was fixed or not, but it was round and smooth, seemed to be in two lobules and seemed to obstruct the bronchus completely. I assume that the collapsed area in the left upper lobe is the portion of the upper lobe that would be aerated through the bronchus that was obstructed by the visualized mass. Is that reasonable, Dr. Hanelin?

DR. HANELIN: I think the whole left upper lobe is reduced somewhat. It may be that the apical division is less aerated than the remainder.

DR. PITTMAN: We have a report of complete obstruction with no air in or out of it.

DR. HANELIN: It is possible, although unlikely, that the entire lobe is represented by the density that we see at the apex, the remainder of the lung being aerated by the lower lobe. The major fissure is not well demarcated.

DR. PITTMAN: Physical examination is not very helpful in this case. There are signs of some diminished tactile fremitus and occasional rales over the right-upper-lobe area, and I suppose that means the extreme upper chest. The diastolic pressure was high, with a nonenlarged heart; I cannot relate it to anything. The liver edge was two finger-breadths below the costal margin and fairly low. I doubt whether that is significant enlargement, and I assume that the rubbery prostate, which was three times the normal size, represented benign hypertrophy.

The blood on examination was fairly good, with a hemoglobin of 12.5 gm. The white-cell count of 20,000, I assume, was a reflection of some infection in the lung. No sputum examination is noted. That is the story. He had been examined on the outside and following bronchoscopy came in for operation.

What was believed to be the matter, and what was the preoperative diagnosis? If we go back to the very first line of this abstract it is stated that the patient was a wool spinner, and I think that means that one should stop and consider what particular things wool spinners might have. They might have dust carried in with the material they were spinning, although that gives an entirely different diffuse, bilateral picture, and I do not think dust was important in this case. I suppose one must mention in the discussion of a patient who works with wool what we were taught in our youth about anthrax; it gives a pneumonic type of process and is acutely fatal. I believe that we do not have to consider it here.

From reading the record, possibly one should give consideration to a foreign body that had been in the bronchus for a long time and had become covered with tissue. I think that that is extremely far-fetched. One should have more sepsis. The fact that there is no history does not rule it out, but in a man of this age it makes it much less likely.

Then we come down, obviously, to a new growth, because here is a mass that occluded the lumen of a bronchus. First to consider is a malignant new growth. There had been no change in this man's x-ray films as far as we can tell for something over

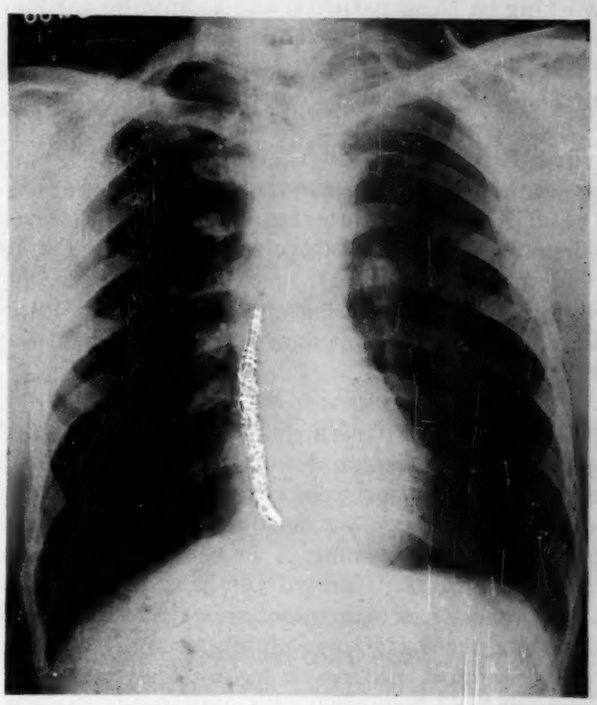

FIGURE 1.

two years. I cannot conceive of a bronchial carcinoma not progressing over a two-year period. In addition, this was a round, smooth mass. We do not know about fixation because it could not be touched. It was quite removed from the carina, but there was no widening or fixation of the carina, and if some lesion of that type had been present for over two years, it seems to me, there would have been extension that would have changed the appearance of the carina.

That brings me down to a benign intrabronchial lesion, which seems to me to fit this story best. The patient had nonspecific bronchial trouble. Probably, he had a good deal of blood streaking, which is extremely common in these tumors. He was not invalided by his disease. Two and a half years or three years before admission he had enough trouble so that an x-ray film was taken but not enough trouble so that he was willing to follow advice, because as a result of the x-ray findings he was told that he should be hospitalized. He probably was not very sick. It seems to me that in a sixty-two-

year-old man, with a rather long history, minimal symptoms, repeated though apparently not very important hemoptysis, and in reasonably good health, the most logical explanation is a benign adenoma in the bronchus, the parenchymal lung disease representing collapse distal to the mechanical obstruction. I shall therefore make that my diagnosis.

DR. DONALD S. KING: At one time it was believed that adenoma occurs more frequently in females than males. Dr. Ronald Sniffen has been working on these patients, and I think he has found the sex incidence to be about fifty-fifty.

DR. PITTMAN: It still is that way in the literature — more frequent in females.

DR. KING: But not in our series here.

DR. PITTMAN: It also occurs in a slightly younger group than sixty-two years.

DR. KING: I cannot remember having seen an adenoma in a man of sixty-two. We have also had epidermoid carcinomas recently that have hung on for a long time. I know the answer, but I agree that it seems as if this man was fairly well to have had a carcinoma.

DR. J. G. SCANNELL: We arrived at the same point that Dr. Pittman did. We thought that the patient had a benign lesion of the bronchus, although we also considered carcinoma of the lung. In a man of sixty-two we decided to do a lobectomy, preserving as much lung as we could. At operation the tumor mass presented in the main left-upper-lobe bronchus, which was extremely short. It was therefore necessary to go closely around the tumor, leaving almost no free margin. The patient was dyspneic, and because of his age, unless there was an out-and-out malignant tumor, we believed that a pneumonectomy was not justified and relied on the benign character of an adenoma. I have forgotten whether or not we had a biopsy before operation.

DR. TRACY B. MALLORY: Dr. Castleman did a frozen section during the operation, and I believe he reported adenoma.

DR. HANELIN: How much was the left upper lobe reduced in size?

DR. SCANNELL: It was not particularly reduced in size. The operative note says that the chest was opened, disclosing a somewhat collapsed left upper lobe, collapsed chiefly in the apical posterior segment.

CLINICAL DIAGNOSIS

Pulmonary tuberculosis.

DR. PITTMAN'S DIAGNOSES

Benign adenoma, left-upper-lobe bronchus.
Collapse of left upper lobe, with chronic infection.

ANATOMICAL DIAGNOSIS

Bronchial adenoma.

PATHOLOGICAL DISCUSSION

DR. MALLORY: The specimen we received in the laboratory showed an intrabronchial tumor. It was, as predicted, a benign adenoma, which had extended through the tracheal wall. Dr. Scannell, in his operative note, said it was shaped like a collar button, which is a common picture presented by this type of tumor. The upper segment of the lobe showed very extensive dense fibrosis, evidently the result of old organization of a pneumonitis. All the anatomical structures in that area had been rather thoroughly destroyed. The rest of the lobe was small and slightly collapsed.

DR. PITTMAN: That probably was represented by the dense area on the film?

DR. HANELIN: Yes.

DR. MAHLON HOAGLAND: Would a tuberculoma be likely to produce such a picture?

DR. PITTMAN: I have spent a good deal of time in the Treadwell Library, since I received this abstract, trying to find an intrabronchial tuberculoma but did not succeed. That is all I can say. That is why I did not mention it in my discussion.

DR. SCANNELL: Have we had bronchial adenoma with satellite metastatic lymph nodes?

DR. MALLORY: We have had only 1 in our series of cases and we have seen 1 or 2 specimens sent in from elsewhere in which satellite lymph nodes were involved, but never a case with generalized metastasis, although they have been reported in cases in which there is no reason to question the diagnosis.

DR. HOAGLAND: Were any lymph nodes removed with this specimen?

DR. MALLORY: Yes, but they were anthracotic and did not contain tumor.

DR. SCANNELL: The term "adenoma" has bothered me because as I understand it, it is not a gland-forming tumor — just a pseudo-adenoma really.

DR. MALLORY: This present tumor resembled a true adenoma, however, rather more than some do. There were in a few areas cells producing mucin, which is an unusual phenomenon, but I still believe there is no doubt that it should be classified as a benign tumor. The most characteristic of these tumors resemble very closely the histologic structure of carcinoid tumors of the appendix and small intestine. The majority of carcinoids remain localized, a few involve regional lymph nodes, and a very small proportion metastasize. Generally both tumors share this characteristic low grade of malignancy. A second group of tumors, likewise usually classed as bronchial adenomas have the histologic features of some of the better differentiated basal-cell tumors of the skin.

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HERSTEDVESTER

An interesting commentary on the methods by which Denmark handles its problem of the criminal psychopath appeared early this year in the *Lancet*.* According to this article the neurotic person knows that he is not well and wants to recover; the psychotic patient is obviously ill, and his course can be planned for him. The psychopath is more difficult to deal with. He is the only one in the regiment who is in step. Society is against him, and he goes through life creating trouble, challenging anyone and everyone to knock the chip off his shoulder. "If one could assess the human misery produced, it might well be found that the psychopath has a blacker record than either the neurotic or the psychotic."

*Taylor, S. Psychopath in our midst: Danish solution. *Lancet* 1:32-34, 1949.

A problem in politics, according to the author, is to prevent psychopaths from reaching the top. This could not be done in Germany; in Britain it has been solved "by making the top comparatively unattractive." Psychopathy and genius are in juxtaposition, and it is hard sometimes to draw the line between them. The genius, however, has the capacity for perseverance.

The Danes, an essentially rational people, have developed their own method for dealing with persons who commit criminal acts as part of the behavior pattern associated with psychopathic personality, as contrasted with the true psychoses. For them, when the times are too disastrously out of joint, the Psychopathic Prison, a modern prison colony, has been for some time in operation at Herstedvester, near Copenhagen, and here, under Section 17 of the Criminal Law of 1930, mentally abnormal criminals who do not have deep-seated mental disease are incarcerated.

The important points that distinguish this institution from other prisons are that it is designed for treatment and for education in self-discipline. Sentences are indeterminate; the prisoner can only be released by the same court that convicted him, and usually on the recommendation of the medical superintendent. Release from prison is always on parole, and release from parole is also on the order of the original court.

Despite the fact that the prison population at Herstedvester represents "a sample of the wickedest people in Denmark," a 50 per cent rate of cure is experienced. This is largely due to the eventual appreciation by the prisoners of the stern fact that the only way they can get out and stay out is by learning to become reasonably acceptable members of society. Cause and effect are simply and regularly demonstrated. Those who work earn money and can buy tobacco and newspapers and cakes on Sundays. Those who will not work soon see the difference.

Castration is one of the conditions of release of incorrigible male sex offenders (who, as a civilized refinement, are refurnished with glass testicles), just as numbers of the inmates of mental-deficiency institutions have been sterilized before release;

not for eugenic reasons but in order that they may re-enter society without increasing society's burdens.

In view of the exposé of current penal methods that has been revealed to the citizens of Massachusetts in recent months, the penal code of Denmark has much to recommend it.

STRANGE BEDFELLOWS

BRITAIN'S "most noted radiologist," according to Bulletin No. 429 of the Citizens Medical Reference Bureau Inc., of 1860 Broadway, New York City, is opposed to mass x-ray checkups. In the words of Dr. James F. Brailsford, founder of the British Radiological Association and director of the x-ray and radium departments at Birmingham Hospital, as reprinted from the Los Angeles *Times*:

> If you feel fit and well, stay away from all doctors. Even in the case of cancer, nature will notify educated persons when to seek medical advice. Mass x-ray examinations for tuberculosis and cancer do more harm than good. Periodic examinations of those who have no symptoms of tuberculosis and cancer are of doubtful value.

"Most people know it when they have cancer," according to Dr. Brailsford's novel creed. "The trouble is that even doctors, knowing they have cancer, keep quiet until too late. . . . However, if people will seek advice when they feel sick and not worry when they feel well. . . lives, money and time will be saved."

The distinguished visitor from Great Britain, who expressed his views as quoted above to a group of physicians at the Hollywood Presbyterian Hospital, is undeniably entitled to his own opinions and the right to express them. It is unfortunate, however, that opinions so contrary to those held by the majority of conscientious physicians should receive any widespread publicity.

The secretary of the Citizens Medical Reference Bureau, Inc., which has so quickly rallied to Dr. Brailsford's unique standard, states, in reply to a request for information, that this organization is a lay one, having for its purpose, "To preserve, establish, maintain and safeguard through publicity and other lawful means, the right of adults or, in the case of minors, the right of parents or guardians to determine the form or manner of treatment or care to be prescribed or applied for the cure or prevention of disease."

Certain of the objectives of the Citizens Medical Reference Bureau are undoubtedly praiseworthy. Where it loses its perspective and departs from its apparently laudable purpose is in maintaining for a primary object not the protection of the rights of the majority to enjoy, so far as possible, freedom from exposure to disease, but what it considers to be the right of the individual to escape vaccination and any other compulsory measures that are designed to prevent him from becoming a menace to the public. What citizens of this type invariably fail to understand is the necessity, in a working democracy, for all members of society to surrender certain personal liberties the exercise of which may jeopardize the common good.

The members of Citizens Medical Bureau, Inc., like those friendly foes of medical practice, the Christian Scientists, happen at the moment to be aligned with the medical profession in its opposition to compulsory health insurance.

Politics makes strange bedfellows, even if only for a night.

GREAT BRITAIN'S AMENDING BILL

ENGLAND'S Minister of Health has submitted to Parliament his promised bill for amending the National Health Service Acts of 1946 and 1947. "Let it be said at once," the *Lancet*[1] reports, "that the Minister has fully kept faith; for all the promises made a year ago are here translated into legal form."

The manner in which a general practitioner may be remunerated is safeguarded by a clause that makes it impossible to change this remuneration by regulation and to make it consist wholly or mainly of a fixed salary without reference to the number of patients for whom he has agreed to provide services. Clause 11 bans any requirement that all specialists employed for the purpose of hospital and specialist services shall be employed whole time.

The position of partnerships and the transfer of practices is clarified, "and appropriate methods are provided for transferring the share of a retir-

ing or deceased partner to the remaining partners." Provision is made for partners who originally stayed out of the Service because of the lack of these new safeguards, to join it for the first two months after the passage of the Bill and receive compensation for the good will of their practices.

Various other amendments to the Act give substance to the promises that had been made — promises that last year were instrumental in finally inducing a majority of the medical profession to accept the terms of employment established under the Act.

There have been many warnings regarding the harm that British physicians believe medical practice has suffered as a result of the Act. The Amending Bill appears as evidence of good faith on the part of the Ministry to make the practice of medicine as acceptable as possible to all who are concerned with it. The *British Medical Journal*, mouthpiece of the British Medical Association, takes a somewhat different attitude. Many more matters were to have been included in the Amending Bill, and in their omission the Minister has failed to fulfil his promise to discuss their inclusion with the medical profession. "He has again committed a breach of trust," the *Journal* insists, "with a profession that has loyally collaborated with the Government in operating a Service full of imperfections." A final answer cannot yet be given to the question whether governmental control of medicine can in any way be made compatible with reasonable efficiency and economy.

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1. Leading Article. Amending bill. *Lancet* **1**:873, 1949.
2. Leading Article. Amending bill. *Brit. M. J.* **1**:904, 1949.

IN HOC SIGNO

The leopard, according to a remote biologic authority, can no more change his spots than can the Ethiopian his skin. The allusion, however, put originally in the form of a question, applies only to the individual and to a pre-Darwinian concept of the nature of things; change is inherent in all life and that form of life can survive the longest that can best adapt itself to its changing environment.

So it is with journalism, which, like lava, frequently the result of an explosive eruption, must remain fluid if it expects to get anywhere.

The *New England Journal of Medicine*, as a familiar example, has changed a number of its spots in its hundred-odd years of existence. Its changes have been gradual, however, as considered changes should be; perhaps its progress may be likened to that of a glacier rather than a stream of lava, and certainly the melting glacier gives off many streams of water whereas the lava carries only destruction in its teeth.

In the files of the *Journal* a distinguished ancestry lies preserved. The *New England Journal of Medicine and Surgery and the Collateral Branches of Science*, "Conducted by a Number of Physicians," was first proposed by Dr. John Collins Warren and made its initial appearance in January, 1812, the leading article consisting of "Remarks on Angina Pectoris" by John Warren.

In 1823 *The Boston Medical Intelligencer*, a weekly publication, appeared, conducted by Jerome V. C. Smith. It contained "Extracts from Foreign and American Journals; A Variety of Local Intelligence on Subjects Connected with Medicine; Biographical Sketches of Distinguished Surgeons and Physicians; Descriptions of the Principal Hospitals in Europe; Original Articles on Various Diseases; with Concise Views of the Improvements and Discoveries in the Medico-Chirurgical Sciences."

The charms of the *Intelligencer* completely overcame the *New England Journal of Medicine and Surgery*. After a short courtship they were united in February, 1828, the synchronous result of the union being the *Boston Medical and Surgical Journal*, born on the nineteenth day of the same month.

Many changes in type, format and substance, but never a lapse in virtue, marked the peaceful, century-long progress of the *Boston Medical and Surgical Journal*. Of these changes the latest were its acquisition by the Massachusetts Medical Society in 1921, and the assumption of its present title in 1928. The *New England Journal of Medicine* has itself undergone conservative changes. The type has been improved, both of the text and of the title. The cover has gone mildly into the red, even if only on alternate weeks. Other minor alterations have

been recommended by the experts and are going into effect with the current volume: a weekly index of our loyal advertisers, and an insigne, adopted after much deliberation, that is truly representative of the *Journal* itself and its distinguished, if somewhat provincial, ancestry. The final form of the seal now appearing on the cover was suggested and drafted by Dr. Harold Bowditch.

In hoc signo vinces or — something like that!

It would be absolute madness, indeed, to trust a confirmed cholera patient to a few drops of camphor spirits, or three grains of *sulphur and charcoal.*

He who depends
Upon such favors, swims with fins of lead,
And hews down oaks with rushes.

Boston M. & S. J., July 4, 1849

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

WOOD-TICK STUDY IN 1949

Some further progress will be made on the wood-tick study during the present season, although it was not possible to get into the field when the ticks first emerged, because funds had not been made available.

The funds that will be used this year represent the small balance left over from the study authorized in 1948. They will be used largely in determination of the results of spraying by other agencies in areas where ticks are prevalent, since it will not be possible for the Department to do any spraying studies this year with the small amount of funds. It is expected that the Legislature will make additional funds available for studies to be carried out in 1950. If so, experiments on the control can be begun as soon as the ticks begin to emerge from hibernation in order to study how long sprays will be effective in keeping down the tick population.

The Department is very much interested in receiving information from any persons or organizations that attempt to control ticks by sprays during the present season. It wishes to have on hand the best information regarding the possible methods of control so that those who expend their funds for the purpose will derive the greatest benefit from their operations.

The Department is particularly anxious to obtain information and receive specimens of ticks found inland more than fifteen miles from the seacoast. Up to the present time most of the tick-infested areas have been located near the coast.

UNUSUAL SEROLOGIC TESTS

Some of the unusual serologic tests formerly performed at the National Institutes of Health are now being done entirely at the Communicable Disease Center in Georgia. These are tests for amebiasis, trichinosis, echinococcosis and leptospirosis. Specimens for these tests should hereafter be sent to the Immunology-Serology Laboratory, Communicable Disease Center, United States Public Health Service, Chamblee, Georgia.

Blood specimens for serologic tests for trypanosomiasis, schistosomiasis, filariasis, leishmaniasis and toxoplasmosis should still be sent to the Laboratory of Tropical Diseases, National Institutes of Health, Bethesda 14, Maryland.

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR MAY, 1949

RÉSUMÉ

DISEASE	MAY 1949	MAY 1948	SEVEN-YEAR MEDIAN
Chancroid	4	2	2*
Chicken pox	2233	1612	1763
Diphtheria	42	14	16
Dog bite	1472	1237	1289
Dysentery, bacillary	4	8	8
German measles	1243	132	381
Gonorrhea	254	218	340
Granuloma inguinale	0	0	0*
Lymphogranuloma venereum	0	2	2*
Malaria	2	1	12
Measles	2327	5743	5320
Meningitis, meningococcal	4	5	16
Meningitis, Pfeiffer-bacillus	1	5	2
Meningitis, pneumococcal	0	2	4
Meningitis, staphylococcal	1	0	0
Meningitis, streptococcal	0	1	1
Meningitis, undetermined	3	4	4
Mumps	1057	2403	1459
Poliomyelitis	10	0	1
Salmonellosis	2	6	6
Scarlet fever	649	908	1120
Syphilis	216	182	539
Tuberculosis, pulmonary	243	207	279
Tuberculosis, other forms	23	11	18
Typhoid fever	6	5	2
Undulant fever	4	4	4
Whooping cough	389	132	537

*Five-year median.

COMMENT

Diseases above the seven-year median were chicken pox, diphtheria, German measles, poliomyelitis and typhoid fever. Diseases below the seven-year median were measles, meningitis, mumps, scarlet fever and whooping cough.

Diphtheria continued to be unusually prevalent, remaining at the level of fifteen years ago for this season. The incidence of poliomyelitis was the highest for May since 1936, but 6 of the cases were widely scattered along the seacoast. German measles continued its upward trend, suggesting that the next season may bring an epidemic.

GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Diphtheria was reported from: Beverly, 1; Boston, 26; Cambridge, 6; Canton, 1; Malden, 2; New Bedford, 2; Newton, 1; Shirley, 1; Somerville, 1; Winthrop, 1; total, 42.

Dysentery, bacillary, was reported from: Pittsfield, 1; Waltham, 2; Winthrop, 1; total, 4.

Encephalitis, infectious, was reported from: Lowell, 1; Rehoboth, 1; Sterling, 1; total, 3.

Infectious hepatitis was reported from: Lowell, 1; Norwood, 1; Wrentham, 2; total, 4.

Malaria was reported from: Lowell, 1; Swampscott, 1; total, 2.

Meningitis, meningococcal, was reported from: Agawam, 1; Boston, 1; Lawrence, 1; Needham, 1; total, 4.

Meningitis, Pfeiffer-bacillus, was reported from: Brockton, 1; total, 1.

Meningitis, staphylococcus, was reported from: Wrentham, 1; total, 1.

Meningitis, undetermined, was reported from: Arlington, 1; Brockton, 1; Taunton, 1; total, 3.

Poliomyelitis was reported from: Arlington, 1; Braintree, 1; Brookline, 1; Cambridge, 1; Milton, 4; Newbury, 1; Wareham, 1; total, 10.

Salmonellosis was reported from: Leominster, 1; Peabody, 1; total, 2.

Septic sore throat was reported from: Boston, 2; Lynn, 1; Worcester, 1; total, 4.

Typhoid fever was reported from: East Longmeadow, 1; Everett, 2; Leominster, 1; Peabody, 1; Somerville, 1; total, 6.

Typhus fever was reported from: Boston, 1; total, 1.

Undulant fever was reported from: Boxboro, 1; Maynard, 1; Natick, 1; Pepperell, 1; total, 4.

MISCELLANY

BOSTON UNIVERSITY ORGANIZES DEPARTMENT OF LEGAL MEDICINE

Dr. Walter Jetter, pathologist for the Massachusetts Department of Mental Health and assistant professor of legal medicine at Harvard Medical School, has been selected by the trustees of Boston University to head a new department of legal medicine at Boston University School of Medicine. He will assume his new duties on July 1.

Dr. Jetter was born in Buffalo, New York, on September 4, 1905. He received his M.D. degree from the University of Buffalo School of Medicine in 1931 and his M.S. in medicine in 1938 from the same school.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Ärztliche Rheokardiographie. By Wolfgang Holzer and Kurt Polzer. 8°, paper, 144 pp., with 88 illustrations and 3 tables. Vienna: Verlag Wilhelm Maudrich, 1948. $3.00. *Bücherei der physikalischen Medizin.* Volume III.

This monograph is comprehensive in scope, discussing the method in general, animal experimentation and the normal rheocardiogram in man, and in diseased conditions of the heart. The pertinent literature is noted throughout the text, which is concluded with an extensive bibliography of sources mentioned in the text and dating to 1947. There is a good index. The material is well arranged. The monograph is well published in a typical German style. It should be available to all persons interested in cardiology.

Bacterial and Mycotic Infections of Man. Edited by René J. Dubos, Ph.D., The Rockefeller Institute for Medical Research. 4°, cloth, 785 pp., with 101 illustrations, including 3 plates in color. Philadelphia: J. B. Lippincott Company, 1948. $5.00.

This comprehensive treatise on medical bacteriology is a companion volume to *Viral and Rickettsial Infections of Man*, edited by Dr. Thomas M. Rivers and published by Lippincott in 1948. Thirty-four authors collaborated in the production of the volume. The beginning chapters deal with general principles and are followed by discussions of the various bacteria, spirochetes and mycoses. The concluding chapters are devoted to sterilization, chemotherapy, epidemiology and the cultivation and identification of pathogenic bacteria. The material is well arranged. There are lists of selected references appended to the various chapters. The text is concluded with comprehensive indexes of authors and subjects. The book is well published, but since it weighs nearly 5 pounds a lighter paper, if possible, should have been used. This should be considered an essential reference book for all medical libraries and should be available to all persons interested in bacteriology and bacterial diseases.

The Digestive Tract in Roentgenology. By Jacob Buckstein, M.D., assistant professor of clinical medicine, Cornell University Medical College, visiting roentgenologist (alimentary-tract division), Bellevue Hospital, New York City, attending gastroenterologist, Beth David Hospital, New York City, and consultant in gastroenterology, Central Islip State Hospital, New York. 4°, cloth, 889 pp., with 1030 illustrations. Philadelphia: J. B. Lippincott Company, 1948. $16.00.

This treatise is based on the author's experience of twenty-five years at Bellevue Hospital, where an enormous amount of material was available, and also on his private practice as a gastroenterologist. The material is well arranged. Selected lists of references are appended to the various chapters. The pertinent literature is reviewed in each special chapter. Indexes of authors and of subjects are referred to throughout the text. The volume is well published and is recommended as a standard reference work for all medical libraries and to all roentgenologists.

Virus Diseases of Man. By C. E. van Rooyen, M.D., D.Sc. (Edin.), M.R.C.P. (Lond.), research member and professor of virus infections, Connaught Medical Research Laboratories and School of Hygiene, University of Toronto; and A. J. Rhodes, M.D., F.R.C.P. (Edin.), research associate and professor of virus infections, Connaught Medical Research Laboratories and School of Hygiene, University of Toronto, and consultant in virus infections, Hospital for Sick Children, Toronto. 8°, cloth, 1202 pp., with 43 illustrations. New York: Thomas Nelson and Sons, 1948. $22.50.

This edition of a standard reference work, first published in 1940, has been thoroughly revised in the light of the knowledge of the subject gained during the past ten years. The literature has been surveyed through 1947, with the addition of some papers published during the early months of 1948. Selected references are appended to each chapter. The latest information on two diseases prevalent in the United States, influenza and poliomyelitis, is given at length. All the diseases now attributed to viruses are discussed in detail. The type and printing are good, but the use of a coated paper, making the volume weigh more than 5 pounds, is not justified by the few illustrations. The book should be in all medical libraries and should be available to all general practitioners.

The Commonsense Psychiatry of Dr. Adolf Meyer. Fifty-two selected papers edited, with biographical narrative. By Alfred Lief. 8°, cloth, 677 pp. New York: McGraw-Hill Book Company, Inc., 1948. $6.50.

This volume constitutes a collection of fifty-two papers of Dr. Meyer brought together from scattered sources and reprinted in one volume for convenience for reference purposes. A short biographic sketch precedes the papers. A glossary and an index conclude the volume. The publishing is excellent. The book is recommended for all medical libraries and should be available to all psychiatrists.

Handbook of Medicine for Final Year Students. By G. F. Walker, M.D., M.R.C.P. (Lond.), consulting physician, Peterborough Memorial Hospital. Fourth edition. 12°, cloth, 308 pp. London: Sylviro Publications Ltd., 1948. 25s.

This manual, first published in 1931 and now in its fourth edition, has been thoroughly revised and brought up to date. It covers the whole field of medicine and naturally reflects the British point of view. The small volume is well published.

Occupational Therapy Source Book. Edited by Sidney Licht, M.D. With an introduction by C. Charles Burlingame, M.D., psychiatrist-in-chief, The Institute of Living. 4°, cloth, 90 pp. Baltimore: Williams and Wilkins Company, 1948. $1.00.

Dr. Licht has brought together in this volume ten extracts on occupational therapy in mental diseases from the works of pioneers in the field of psychiatry, ranging from Pinel (1801) to Reid (1914). Other authors represented and the dates of their publications are Reil (1803), Hallaran (1810), Benjamin Rush (1812), Tuke (1816), Esquirol (1838), Leuret

(1840), Voisin (1843) and Kirkbride (1880). The paper of Dr. Reid on "ergotherapy in the treatment of mental disorders" was originally published in the *Boston Medical and Surgical Journal*. The extracts are preceded by a long outline of the early history of occupational therapy, dating from the Hippocratic era to 1915, written by Dr. Licht. The volume is well published, and the price is very reasonable. The book should be in all medical libraries, in all medical-history collections and in the collections of persons interested in the subject.

Pediatrics and the Emotional Needs of the Child: As discussed by pediatricians and psychiatrists at Hershey, Pennsylvania, March 6-8, 1947. Edited by Helen L. Witmer. 8°, paper, 180 pp., with 17 illustrations. New York: Commonwealth Fund, 1948. $1.50.

This conference was participated in by 48 physicians and social workers. The various aspects of the subject were discussed in detail in five meetings. An appendix comprises reports from the psychiatric services or child-guidance clinics of ten prominent hospitals. The volume is well published and should be in all collections on pediatrics, psychiatry and applied psychology. It should prove useful to social workers.

An Introduction to Surgery. By Rutherford Morison, M.D., F.R.C.S. Edin., F.R.C.S. Eng., M.A., D.C.L., LL.D., and Charles F. M. Saint, C.B.E., M.D., M.S., F.R.C.S., F.R.A.C.S. Fourth edition. 8°, cloth, 330 pp., with 304 illustrations. Baltimore: Williams and Wilkins Company, 1948. $10.00.

This small manual, designed for the student of surgery, was revised and brought up to date by Dr. Saint after the death of Dr. Morison. It constitutes on the whole a short work on surgical pathology. The material is well organized, and the text well illustrated. The printing was done in Great Britain, and the publishing is excellent.

A.M.A. Interns' Manual. 12°, cloth, 201 pp. Philadelphia: W. B. Saunders Company, 1948. $2.25.

This small volume was originally published in 1938 under the present title. It was the successor to *Hospital Practice for Internes*, first published in 1932. The text has been prepared by the various councils of the Association, and is divided into seven principal sections, as follows: internships and residencies — general information; clinical and laboratory data, including common emergencies; drug administration; materia medica — useful drugs; acute poisoning (diagnosis and treatment); diet and nutrition; and physical medicine. Parts two to seven supply the intern with the essential facts needed in his daily practice. The eighth part, the "Lawful Scope of Intern Practice," is an important contribution on the legal status of interns in the various states. The last part is a short description of the American Medical Association and its subdivisions. There is an index. The publishing is excellent. The book should prove exceedingly useful to all interns.

NOTICES

MASSACHUSETTS TRUDEAU SOCIETY

At a meeting of the Massachusetts Trudeau Society on June 9, the following officers were elected: president, Henry D. Chadwick, of Waltham; vice-president, Francis P. Dawson, of Waltham, and secretary-treasurer, Edward J. Welch, of Brookline.

SOCIETY MEETINGS AND CONFERENCES

SEPTEMBER 6–10. American Congress of Physical Medicine. Page xiii, issue of March 24.

SEPTEMBER 8. Care of the Terminal Stage of Cancer. Dr. John W. Spellman. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

SEPTEMBER 28–30. Mississippi Valley Medical Society. Page 1060, issue of December 30.

OCTOBER 11–15. American Society of Clinical Pathologists. Drake Hotel, Chicago.

NOVEMBER 2. New England Obstetrical and Gynecological Society. Hotel Somerset, Boston.

NOVEMBER 3–5. American Association of Blood Banks. Page xi, issue of June 16.

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, JULY 14

FRIDAY, JULY 15

*9:00 a.m.–12:00 m. Combined Medical and Surgical Staff Rounds. Peter Bent Brigham Hospital.

*1:30 p.m. Tumor Clinic. Out-Patient Department, Mt. Auburn Hospital, Cambridge.

MONDAY, JULY 18

*11:30 a.m.–12:15 p.m. Chest X-Ray Conference. South End Health Unit, 57 East Concord Street, Boston. Dr. Cleaveland Floyd in charge.

*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.

TUESDAY, JULY 19

*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.

*1:30–2:30 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.

WEDNESDAY, JULY 20

*12:00 m.–1:00 p.m. Clinical Conference (Children's Hospital). Amphitheater, Peter Bent Brigham Hospital.

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